Environmental Protection Authority
Te Mana Rauhī Taiao

DECISION

28 June 2013

1. Summary

Substance	Benevia and Exirel
Application code	APP201204
Application type	To import or manufacture for release any hazardous substance under section 28 of the Hazardous Substances and New Organisms Act 1996 ("the Act")
Application sub-type	Category C
Applicant	DuPont Limited
Purpose of the application	To import Benevia and Exirel, as insecticides for use on various crops
Date application received	16 January 2012
Consideration	Consideration was delayed awaiting the outcome of the OECD Joint Pesticide Review in accordance with section 58 of the Act and consequently the consideration was postponed for 163 working days A time waiver allowed staff additional time for completing the evaluation and review of this application. Consideration of this application was waived until 28 June 2013
Considered by	A decision making committee of the Environmental Protection Authority
Decision	Approved with controls
Approval code	Benevia: HSR100856 Exirel: HSR100857
Hazard classifications (refer to Table 1)	Benevia: 6.5B, 6.9B, 9.1A, 9.4B Exirel: 6.3A, 6.5B, 6.9B, 9.1A, 9.4B

2. Background

2.1. Benevia and Exirel are insecticides containing the active ingredient cyantraniliprole. Benevia is intended for application on potatoes, tomatoes and onions. Exirel is intended for application on brassicas (turnips, swede, forage rape and kale). Both substances will be applied to control a variety of insects on these crops.

2.2. The proposed application is similar to other pesticides currently approved in New Zealand. However, cyantraniliprole is a new active ingredient in New Zealand as it is not currently present in any HSNO approved pesticides.

2.3. The applicant intends to import Benevia and Exirel into New Zealand packed ready for sale.

2.4. The preferred method of disposal of the substance is by application as a pesticide in accordance with the product label.

3. Process, consultation and reasons for notification

3.1. The application was lodged pursuant to section 28 of the Act.

3.2. An OECD Joint Pesticides Review was undertaken recently for cyantrniliprole. Once the review was completed the EPA ("the staff") confirmed that the results of their scientific and technical analysis were consistent with the OECD review findings.

3.3. The Labour Group of the Ministry of Business, Innovation and Employment (MBIE)[1], the Department of Conservation, the Ministry of Health and the Ministry for Primary Industries (Agricultural Compounds and Veterinary Medicines Group) were advised of the application on 20 January 2012 and invited to comment by 14 February 2012. No comments were received.

3.4. In accordance with section 53(2) of the Act, the application was publicly notified on 3 February 2012. This is because under delegation the Chief Executive of the EPA determined that there may be significant public interest in the application because:

- The active ingredient, cyantraniliprole, is new to New Zealand; and
- Benevia and Exirel have a HSNO 9.4B classification (harmful to bees), and there is significant public interest in substances that are toxic to bees.

3.5. One submission was received during the submission period which ended on 19 March 2012. In their submission, Federated Farmers indicated that they support the application based on the potential benefits that the product offers to growers of tomatoes, potatoes and fodder brassicas. However, their submission stressed the need to address the risks to bees and other beneficial species. The committee adopted controls recommended by the staff to limit application patterns for Benevia and Exirel to reduce risks to bees and other beneficial insects.

[1] Formerly the Department of Labour.

4. Hazardous properties

4.1. Cyantraniliprole, Benevia and Exirel are currently the subject of joint international review under the OECD Pesticide Programme. Data for that review was provided by the applicant and reviewed by the Australian, Canadian, and USA regulatory agencies.

4.2. The staff determined most of the hazard classifications below using data submitted to the OECD Pesticide Programme. Other classifications were made using the EPA hazardous substance mixture rules which provide a process for classifying the individual components of a substance. The classifications determined by the staff indicate higher hazards than those submitted by the applicant. The hazard classifications for Exirel were increased for skin irritancy, and decreased for eye irritancy, and classifications were added for both substances for target organ toxicity and invertebrate toxicity (Table 1).

Table 1 Hazard classifications of Benevia and Exirel

Hazard Endpoint	Benevia applicant classification	Benevia EPA classification	Exirel applicant classification	Exirel EPA classification
Skin irritancy	-	-	6.3B	6.3A
Eye irritancy	-	-	6.4A	no
Contact sensitisation	6.5B	6.5B	6.5B	6.5B
Target organ toxicity	-	6.9B	-	6.9B
Aquatic ecotoxicity	9.1A	9.1A	9.1A	9.1A
Invertebrate ecotoxicity	-	9.4B	-	9.4B

The committee has adopted the staff classifications.

5. Risk and benefit assessment

Assessment of risks to human health and the environment

5.1. The staff have evaluated the potential of Benevia and Exirel to cause adverse effects to human health and the environment during all stages of the substances' lifecycles. Quantitative assessments have been undertaken for the use phase of the substances' lifecycles. Qualitative assessments have been undertaken for all other stages of the lifecycles.

5.2. The quantitative and qualitative risk assessments for human health and the environment associated with Benevia and Exirel are set out in Tables 2, 3 and 4. This includes skin irritancy, contact sensitisation, target organ toxicity, aquatic ecotoxicity and terrestrial invertebrate ecotoxicity. A summary of the quantitative risk assessment is also included in these tables. More information about the risk assessment is detailed in Appendix B.

Table 2 Assessment of risks to human health -Benevia

Lifecycle	Description	Likelihood	Magnitude	Matrix	Comment	Level of risk
Manufacture[2] and packaging	Contact sensitisation	Highly Improbable	The magnitude of skin sensitisation is considered minor to moderate based on the sensitivity of the exposed parties	Negligible	Workers handling the substance should be aware of the hazards and the measures that need to be undertaken to ensure their own safety. Manufacturing and packaging facilities in New Zealand will be required to meet the HSNO requirements for equipment, emergency management and Personal Protective Equipment (PPE). Compliance with HSNO information provisions (e.g. labels, advertising, Safety Data Sheets (SDS), and MBIE Health and Safety requirements) will also be required	Negligible
	Target organ toxicity	Highly improbable	Major	Low	While the qualitative risk descriptors indicate a **low** level of risk driven by this chronic effect, the staff advised the committee that processes in New Zealand will be required to meet the HSNO requirements for equipment, emergency management and provision of information as well as Good Manufacturing Practice (GMP) and Health and Safety regulations. The staff consider that meeting these requirements will make the likelihood of exposure that would lead to a chronic effect so highly improbable that the level of risk for the chronic toxic adverse effects is **negligible**	Negligible
Importation, transport, storage	Contact sensitisation	Highly Improbable	The magnitude of skin sensitisation is considered minor to moderate based on the sensitivity of the exposed parties	Negligible	Workers and bystanders will only be exposed to the substance during this part of the lifecycle in isolated incidents where spillage occurs. Compliance with HSNO controls (e.g. labels, SDS) and the Land Transport Rule 45001, Civil Aviation Act 1990 and Maritime Transport Act 1994 (as applicable) is required	Negligible

[2] The applicant intends to import (not manufacture) Benevia and Exirel. However, it is possible that the substances could be manufactured in New Zealand in the future. Consequently, the risks associated with the manufacture of Benevia and Exirel have been evaluated so the approval of these substances will be applicable to both the import and manufacture of Benevia and Exirel.

	Target organ toxicity	The risk of chronic effects from exposure during importation, transport and storage is sufficiently remote that the level of risk will be **negligible**				Negligible
Wide dispersive use (operators and bystanders)	Contact sensitisation	Highly Improbable	The magnitude of skin sensitisation is considered minor to moderate based on the sensitivity of the exposed parties	Negligible	Users: The staff advised the committee that the use of PPE and other relevant controls, such as labelling and packaging, will adequately manage the risks for the users. The staff note that the proposed use pattern for this substance is similar to other approved pesticides Bystanders: The substance must be applied by approved handlers when applied in a wide dispersive manner or by a commercial contractor. Due to the applicators knowledge and experience with pesticides it is not expected that bystanders will be exposed to the substance	Negligible
	Target organ toxicity	Highly improbable	Major	Low	While the chronic toxic properties of this substance could cause major adverse effects to the user, the level of expertise required by the applicator will reduce the effect from voluntary exposure from **low** to **negligible** The staff informed the committee that the use pattern of this substance is similar to a number of existing substances and does not consider that this substance presents a greater risk to users than other substances currently available for similar end use	Negligible
Disposal	Contact sensitisation	Highly Improbable	The magnitude of skin sensitisation is considered minor to moderate based on the sensitivity of the exposed parties	Negligible	It is highly improbable that workers will suffer sensitisation from the substance during disposal, given that the substance will generally be disposed of by use	Negligible
	Target organ toxicity	The risk of chronic effects from exposure during disposal of the substance is sufficiently remote that the level of risk will be **negligible**				Negligible

Table 3 Assessment of risks to human health -Exirel

Lifecycle	Description	Likelihood	Magnitude	Matrix	Comment	Level of risk
Manufacture[3] and packaging	Skin irritation	Highly Improbable	Minimal	Negligible	Workers handling the substance should be aware of the hazards and the measures that need to be undertaken to ensure their own safety. Manufacturing and packaging facilities in New Zealand will be required to meet the HSNO requirements for equipment, emergency management and Personal Protective Equipment (PPE). Compliance with HSNO information provisions (e.g. labels, advertising, Safety Data Sheets (SDS), and MBIE Health and Safety requirements) will also be required	Negligible
	Contact sensitisation	Highly Improbable	The magnitude of skin sensitisation is considered minor to moderate based on the sensitivity of the exposed parties	Negligible		Negligible
	Target organ toxicity	Highly improbable	Major	Low	While the qualitative risk descriptors indicate a **low** level of risk driven by this chronic effect, the staff informed the committee that processes in New Zealand will be required to meet the HSNO requirements for equipment, emergency management and provision of information as well as Good Manufacturing Practice (GMP) and Health and Safety regulations. The staff consider that meeting these requirements will make the likelihood of exposure that would lead to a chronic effect so highly improbable that the level of risk for the chronic toxic adverse effects is **negligible**	Negligible
Importation, transport, storage	Skin irritation	Highly Improbable	Minimal	Negligible	Workers and bystanders will only be exposed to the substance during this part of the lifecycle in isolated incidents where spillage occurs. Compliance with HSNO controls (e.g. labels, SDS) and	Negligible

[3] The applicant intends to import (not manufacture) Benevia and Exirel. However, it is possible that the substances could be manufactured in New Zealand in the future. Consequently, the risks associated with the manufacture of Benevia and Exirel have been evaluated so the approval of these substances will be applicable to both the import and manufacture of Benevia and Exirel.

Lifecycle	Description	Likelihood	Magnitude	Matrix	Comment	Level of risk
	Contact sensitisation	Highly Improbable	The magnitude of skin sensitisation is considered minor to moderate based on the sensitivity of the exposed parties	Negligible	the Land Transport Rule 45001, Civil Aviation Act 1990 and Maritime Transport Act 1994 (as applicable) is required	Negligible
	Target organ toxicity	The risk of chronic effects from exposure during importation, transport and storage is sufficiently remote that the level of risk will be **negligible**				Negligible
Wide dispersive use (operators and bystanders)	Skin irritation	Highly Improbable	Minimal	Negligible	The substance must be labelled to identify its potential risk minimising the opportunity for it to cause toxicity. HSNO requirements for PPE, packaging, identification and emergency management requirements will need to be complied with	Negligible
	Contact sensitisation	Highly Improbable	The magnitude of skin sensitisation is considered minor to moderate based on the sensitivity of the exposed parties	Negligible	Users: The staff advised the committee that the use PPE and other relevant controls, such as labelling and packaging, will adequately manage the risks for the users. The staff note that the proposed use pattern for this substance is similar to other approved pesticides Bystanders: The substance must be applied by approved handlers when applied in a wide dispersive manner or by a commercial contractor. Due to the applicators knowledge and experience with pesticides it is not expected that bystanders will be exposed to the substance	Negligible
	Target organ toxicity	Highly improbable	Major	Low	While the chronic toxic properties of this substance could cause major adverse effects to the user, the level of expertise required by the applicator will reduce the effect from voluntary exposure from **low** to **negligible** The use pattern of this substance is similar to a number of existing substances and that this substance does not present a greater	Negligible

Lifecycle	Description	Likelihood	Magnitude	Matrix	Comment	Level of risk
					risk to users than other substances currently available for similar end use	
Disposal	Skin irritancy	Highly improbable	Minimal	Negligible	The applicant indicates that all attempts should be made to use the substance completely, in accordance with its registered use. Where disposal is necessary the substance must be disposed of in accordance with the requirements of the Hazardous Substances (Disposal) Regulations 2001 and the Resource Management Act 1991	
	Contact sensitisation	Highly improbable	Minimal	Negligible	The staff informed the committeethat it is highly improbable that workers will suffer sensitisation from the substance during disposal, given that the substance will generally be disposed of by use	Negligible
	Target organ toxicity	The risk of chronic effects from exposure during disposal of the substance is sufficiently remote that the level of risk will be **negligible**				Negligible

Table 4 Assessment of risks to the environment- Benevia and Exirel

Lifecycle	Description	Likelihood	Magnitude	Matrix	Comment	Level of risk
Manufacture[4], importation, transport and storage	Death or adverse effects to aquatic organisms	Highly improbable	Major	Low	Compliance with the HSNO controls (and the Land Transport Rule 45001, Civil Aviation Act 1990 and Maritime Transport Act 1994 (as applicable)) will ensure that the potential for any spill is highly improbable. Any spill is likely to lead to localised effects only involving small quantities of the substance	Negligible
Use	Death or adverse effects to aquatic organisms	Quantitative assessment indicates that the acute and chronic risks to aquatic organisms from use of the substance are low, based on the proposed use patterns for New Zealand. The staff recommended to the committee that the application of, and compliance with, additional controls (e.g. restricting application of the substance into or onto water) will ensure that these risks are mitigated and are therefore negligible				
	Death or adverse effects to soil organisms	Quantitative assessment indicates that the acute and chronic risks to soil organisms including earthworms from use of the substance are low, and therefore are considered negligible.				
	Death or adverse effects to non-target plants.	Quantitative assessment indicates that the substance does not have any phytotoxic activity, and therefore the risks to non-target plants are considered negligible				
	Death or adverse effects to terrestrial vertebrates	Quantitative assessment indicates that the acute and chronic risks to birds from use of the substance are low, and therefore are considered negligible				
	Death or adverse effects to terrestrial invertebrates	Honeybees - Exirel presents a low oral risk to honeybees based on the standard acute risk assessment methodology and Benevia presents a high oral risk. Benevia and Exirel present a low acute risk to honeybees from contact exposure. Staff advised the committee that some sub-lethal effects occurred in surviving bees in both the oral and contact toxicity				

[4] The applicant intends to import (not manufacture) Benevia and Exirel. However, it is possible that the substances could be manufactured in New Zealand in the future. Consequently, the risks associated with the manufacture of Benevia and Exirel have been evaluated so the approval of these substances will be applicable to both the import and manufacture of Benevia and Exirel

		tests. At this time, the risk assessment methodology is not available to determine the significance of those observed effects. Likewise, in the higher tier tests with honeybees, the possibility of adverse effects cannot be excluded with no standardised methodology currently available to further evaluate risks from exposure in the field. Some short-term effects on behaviour or mortality were observed in semi-field tests. Impacts on brood development were generally not observed, though it was noted that in many cases the brood assessments were only conducted once before and once after application, which is not sufficiently long enough to derive endpoints regarding colony strength and brood development Overall quantitative assessment indicates that the risks to bees and other arthropods from use of the substances are low, and with the addition of label statements limiting application times they are considered to be negligible.				
Disposal	Death or adverse effects to aquatic or terrestrial organisms	Highly improbable	Minor	Negligible	The applicant indicates that all attempts should be made to use the substance completely in accordance with its registered use. Where disposal is necessary, the substance must be disposed of in accordance with the requirements of the Hazardous Substances (Disposal) Regulations 2001	Negligible

Relationship of Māori to the environment

5.3. The staff have considered the potential of Benevia and Exirel to cause adverse effects to the relationship of Māori to the environment. The class 6 and 9 classifications noted in Table 1 raise the potential for the use or management of Benevia and Exirel to lead to the deterioration of the mauri of people (individually and collectively), and of terrestrial and aquatic taonga species (particularly native birds, soil organisms and pollinating insects). In doing so, it also has the potential to inhibit the ability of Māori to fulfil their kaitiakitanga duty to manage the health and wellbeing of taonga for future generations.

5.4. Based on the assessment for Benevia and Exirel outlined in Tables 2, 3 and 4 above, and when considering information provided relating to use and management, the staff consider that the risks to Māori culture or traditional relationships with ancestral lands, water, sites, wāhi tapu, valued flora and fauna or other taonga are likely to be negligible. This is particularly the case with additional controls in place relating to the prohibition of the use of Benevia and Exirel into, onto or over water, and in relation to restrictions on application rates, methods, frequency and timing.

5.5. Given this assessment, there is no evidence to suggest that the use of Benevia and Exirel in accordance with controls will breach the principles of the Treaty of Waitangi.

Assessment of risks to society, the community and the market economy

5.6. No adverse effects to society, communities or the market economy have been identified as a result of the approval of this substance, provided the use, storage and transport of Benevia and Exirel is compliant with the controls specified in this approval. Human health and environmental effects are assessed in Tables 2, 3 and 4 below, and the staff recommended to the committee that no further assessment is necessary.

New Zealand's international obligations

5.7. The committee did not identify any international obligations that that may be impacted by the approval of Benevia and Exirel.

Overall assessment of risks

5.8. The committee has taken the view that, with controls in place, the risks associated with Benevia and Exirel are negligible.

Identification of benefits

5.9. The applicant considers that Benevia and Exirel will control a variety of insect pests. This will increase yield and ensure high quality crops which will provide benefits to farmers, the local community and the New Zealand economy. Cyantraniliprole is a new active ingredient. The availability of different pesticides will help minimise disease resistance.

The effects of the substance being unavailable

5.10. The staff advised the committeethat a likely effect of the substances being unavailable is that less consumer choice will result in less competitive pricing. In addition, fewer pesticide choices may result in greater disease resistance in crops.

Overall assessment of benefits

5.11. The committee are satisfied that the availability of Benevia and Exirel will provide benefits to New Zealand including economic benefits for some businesses, greater consumer choice and a reduction in disease resistance.

6. Controls

6.1. Based on the hazard classifications determined for Benevia and Exirel (Table 1, Section 4), a set of associated default controls specified by regulations under the Act has been identified. The default controls form the basis of the controls set out in Appendix C. The committee has adopted the staff's risk assessment, and considers that the following exposure limits are relevant and that the additions, variations and deletions set out below should be applied to Benevia and Exirel.

The setting of exposure limits

6.2. Tolerable Exposure Limits (TELs) can be set to control hazardous substances entering the environment in quantities sufficient to present a risk to people. No Tolerable Exposure Limits (TELs) have been set for any components of Benevia and Exirel at this time as the level of risk to bystanders is considered negligible.

6.3. The following Acceptable Daily Exposure (ADE) and Potential Daily Exposure (PDE) values have been set for cyantraniliprole:

- ADE = 0.01 mg/kg bw/day
- PDE_{food} = 0.007 mg/kg bw/day
- PDE_{Water} = 0.002 mg/kg bw/day
- PDE_{Other} = 0.001 mg/kg bw/day

6.4. The EPA typically adopts Workplace Exposure Standard (WES) values (listed in MBIE's Workplace Exposure Standards document[5]) to control exposure in places of work.

6.5. MBIE has not set a WES value for cyantraniliprole or for any component of Benevia. However, the MBIE WES for component G of Exirel has been applied to this approval.

[5] http://www.osh.dol.govt.nz/publications/booklets/wes-2013/wes-and-biological-indices-2013.pdf

6.6. The default controls allow the setting of Environmental Exposure Limits (EELs) to control hazardous substances entering the environment in quantities sufficient to present a risk to the environment. EELs have not been proposed for any component of Benevia or Exirel at this time as the level of risk to the environment is considered to be negligible. The default EEL values have therefore been deleted by the committee.

6.7. The default controls require the EPA to set an application rate for a class 9 substance which is to be sprayed on an area of land (or air or water) and for which an EEL has been set. As no EEL has been proposed for Benevia or Exirel, a maximum application rate is not required to be set under regulation 48 of the Hazardous Substances (Classes 6, 8, and 9 Controls) Regulations 2001. However, environmental exposure modelling undertaken by EPA staff indicates there may be a risk to aquatic organisms and terrestrial invertebrates when the substance is used according to the label requirements. It is therefore considered appropriate by the committee under section 77A to set a maximum application rate for mitigating those risks.

Additional controls

6.8. The staff note and the committee agreed that the risk quotients derived from the quantitative environmental exposure modelling indicate that restrictions on use are necessary to mitigate the risks Benevia and Exirel present to aquatic and terrestrial environments. Accordingly, it is considered that the application of controls addressing these risks will be more effective than the default controls in terms of their effects on the management, use and risks of the substance. Consequently, the following additional controls adopted by the committee are applied to Benevia and Exirel to restrict the level of risk to the environment:

- Benevia and Exirel must not be applied onto, into or over water[6];
- Application of Benevia and Exirel must not exceed a maximum application rate of 50 g cyantraniliprole/ha, at a maximum application frequency of three times per year, with a minimum of 7 days between applications;
- Use of Benevia and Exirel must be by ground-based methods[7] only;
- Spray Benevia in flowering crops only after daily honeybee flights, unless the application rate is less than or equal to 20 gai/ha and spraying after daily honeybee flights is not possible
- Spray Exirel in flowering crops only after daily honeybee flights, unless spraying after daily honeybee flights is not possible
- Ensure flowering weeds are removed before spraying Benevia and Exirel to avoid potential exposure of honeybees

[6] Where "water" means water in all its physical forms, whether flowing or not, and whether over or under ground, but does not include water in any form while in a pipe, tank or cistern, or water used in the dilution of the substance prior to application, or water used in the dilution of the substance prior to application, or water used to rinse the container after use.

[7] Ground-based methods of applying pesticides include, but are not limited to, application by ground boom, airblast or knapsack, and do not include aerial application methods

- Ensure spray drift is avoided into flowering off-crop habitats during the application of Benevia

6.9. The commiteenote that the default controls do not address the risks associated with storage or use of substances within stationary container systems (e.g. tanks). These risks include the failure of primary containment resulting in a large spill of the substance into the environment. In addition, the default controls do not allow for dispensation where it is unnecessary for any pipework associated with the stationary container systems to have secondary containment. Accordingly, the application of controls addressing these risks is considered more effective than the default controls in terms of their effect on the management, use and risks of the substance. The revised controls are shown in Appendix C.

Variation and deletion of controls

6.10. The default controls include requirements for secondary containment of pooling substances (Regulations 35-41 of the Hazardous Substances (Emergency Management) Regulations 2001). The risks associated with the containment of substances which are not class 1 to 5 substances (i.e. do not ignite or explode) are different to those associated with class 1 to 5 substances. Consequently the secondary containment requirements can be modified for Benevia and Exirel, as specified in Appendix C. These modified secondary containment measures are considered adequate to manage the risks of a spillage of Benevia or Exirel, therefore, this variation is considered more cost-effective in terms of managing the risks of the substances.

Review of controls for cost-effectiveness

6.11. The committee consider that the proposed controls are the most cost-effective means of managing the identified potential risks and costs associated with this application. The applicant was given an opportunity to comment on the proposed controls as set out in this decision. The applicant indicated that they had no concerns with the proposed controls.

7. Environmental user charges

7.1. The committee consider that use of controls on Benevia and Exirel is an effective means of managing risks associated with these substances. Therefore, it is not considered necessary to apply environmental user charges to these substances as an alternative or additional means of achieving effective risk management. Accordingly, no report has been made to the Minister for the Environment.

8. Conclusion

8.1. Taking into account the staff's assessment of the potential risks and benefits associated with Benevia and Exirel (see Section 5), the Committee considers that, with controls in place:

- the risks to human health and the environment arising from the hazardous properties of Benevia and Exirel (being contact sensitisation, target organ toxicity and aquatic ecotoxicity, see Table 1, Section 4) are ***negligible***;
- significant adverse impacts on the social or economic environment associated with Benevia and Exirel use are not anticipated;
- significant adverse impacts on Māori culture or traditional relationships with ancestral lands, water, sites, wāhi tapu, valued flora and fauna or other taonga associated with the use of Benevia and Exirel are not anticipated;
- breaches of the principles of the Te Tiriti o Waitangi/Treaty of Waitangi associated with the use of Benevia and Exirel are not anticipated;
- benefits will be derived for New Zealand by allowing the use of Benevia and Exirel.

9. Decision

9.1. Pursuant to section 29 of the Act, the Committee has considered this application to import or manufacture hazardous substances for release made under section 28 of the Act and have applied the relevant sections of the Act and clauses of the Hazardous Substances and New Organisms (Methodology) Order 1998 ("the Methodology") as detailed in the decision path and explanatory notes available from the EPA website[8].

9.2. The Committee is satisfied with the hazard classifications identified by the staff in Table 1 (Section 4) and accordingly confers them on Benevia and Exirel.

9.3. The Committee considers that, with controls in place, the risks to human health and to the environment will be properly managed, and there will be benefits associated with the release of Benevia and Exirel. Therefore, the Committee considers that it is evident that the application may be approved in accordance with clause 26, with the controls proposed by the staff and documented in Appendix C.

9.4. As the manufacture of Benevia and Exirel would not impose any additional risks over the importation of the substance, this approval should apply to both importation and manufacture of Benevia and Exirel.

9.5. The importation and manufacture of the hazardous substance, Benevia and Exirel, is thus approved with controls as listed in Appendix C.

	Date:
Val Orchard **Chair, Decision-making Committee EPA**	

[8] http://www.epa.govt.nz/publications/er-pr-02-decision-paths.pdf

Appendix A: Staff classification of Benevia and Exirel and cyantraniliprole

The active ingredient cyantraniliprole, and the formulations of Benevia and Exirel, have been the subject of full review by the OECD Joint Pesticides review team.

The EPA staff accepted the conclusions of the OECD review and have not further checked the test endpoints presented in the EU documents. Unless otherwise stated, all endpoint data summarised in this document were sourced from the relevant section of those review reports and were fully compliant with the relevant international test methods. For full details of testing undertaken, reference has to be made to OECD documents.

The assessment of risks to people and the environment in New Zealand from the use of Benevia and Exirel, were undertaken by the EPA staff using the endpoint data available and the standard risk assessment methodologies used by the EPA in any other Category C application.

Data quality – overall evaluation

The EPA has adopted the Klimisch *et al* (1997)[9] data reliability scoring system for evaluating data used in the hazard classification and risk assessment of chemicals.

The staff have assigned Klimisch data reliability scores to submitted studies.

The staff acknowledge that there are frequently data gaps in the hazard classification for chemicals which have been in use internationally for a long time. International programmes such as the OECD High Production Volume programme[10], REACH[11], and European Regulation 1107/2009/EC[12] are progressively working towards filling these data gaps. As new information becomes available, staff will update the Hazardous Substances and New Organisms (HSNO) classifications for those substances.

[9] Klimisch, H-J., Andrear, M., & U. Tillmann, 1997. A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. Reg. Toxicol. Pharmacol. 25**,** 1–5 (1997)
[10] http://www.icca-chem.org/Home/ICCA-initiatives/High-production-volume-chemicals-initiative-HPV/
[11] http://ec.europa.eu/environment/chemicals/reach/reach_intro.htm
[12] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:309:0001:0050:EN:PDF

Table 5 Summary of the applicant's and staff's hazard classification of cyantraniliprole, Benevia and Exirel

Hazard Class Subclass	Classifications						Method of classification (formulations)		Remarks
	Cyantraniliprole		Benevia		Exirel				
	Applicant	Staff	Applicant	Staff	Applicant	Staff	Test data	Mixt. rules	
Class 1 Explosiveness	No	No	No	No	No	No	☒	☐	
Class 2, 3 & 4 Flammability	No	No	No	No	No	No	☒	☐	
Class 5 Oxidisers/Organic Peroxides	No	No	No	No	No	No	☒	☐	
Subclass 8.1 Metallic corrosiveness	No	No	No	No	No	No	☒	☐	
Subclass 6.1 Acute toxicity (oral)	-	No	No	No	No	No	☒	☐	
Subclass 6.1Acute toxicity (dermal)	-	No	No	No	No	No	☒	☐	
Subclass 6.1 Acute toxicity (inhalation)	-	No	No	No	No	No	☒	☐	
Subclass 6.1 Aspiration hazard	-	ND	-	ND	-	ND	☐	☐	
Subclass 6.3/8.2 Skin irritancy/corros-ion	-	No	No	No	6.3B	6.3A	☒	☐	Erythema and desquamation persisted for 14 days with Exirel
Subclass 6.4/8.3 Eye irritancy/corros-ion	-	No	No	No	6.4A	No	☒	☐	Mean Draize Scores for Exirel were well below the

Hazard Class Subclass	Classifications						Method of classification (formulations)		Remarks
	Cyantraniliprole		Benevia		Exirel				
	Applicant	Staff	Applicant	Staff	Applicant	Staff	Test data	Mixt. rules	
									threshold for classification. It is unclear why applicant proposed 6.4A: study report notes findings indicate classification in USEPA category III, but not under EU or GHS
Subclass 6.5A Respiratory sensitisation	-	ND	No	ND	No	ND	☐	☐	
Subclass 6.5B Contact sensitisation	-	No	6.5B	6.5B	6.5B	6.5B	☒	☐	
Subclass 6.6 Mutagenicity	-	No	No	ND	No	ND	☐	☒	
Subclass 6.7 Carcinogenicity	-	No	No	ND	No	ND	☐	☒	
Subclass 6.8 Reproductive/ developmental toxicity	-	No	No	ND	No	ND	☐	☒	
Subclass 6.8 Reproductive/ developmental toxicity (*via* lactation)	-	No	No	ND	No	ND	☐	☒	
Subclass 6.9 Target organ systemic toxicity	-	6.9B	No	6.9B	No	6.9B (oral and	☐	☒	Benevia: components A and G_3

Hazard Class Subclass	Classifications						Method of classification (formulations)		Remarks
	Cyantraniliprole		Benevia		Exirel				
	Applicant	Staff	Applicant	Staff	Applicant	Staff	Test data	Mixt. rules	
						inha-lati-on)			Exirel: Components A (oral), C (inhalation) and H_3
Subclass 9.1 Aquatic ecotoxicity	-	9.1A	9.1A	9.1A	9.1A	9.1A	☒	☐	
Subclass 9.2 Soil ecotoxicity	-	No	No	No	No	No	☒	☐	
Subclass 9.3 Terrestrial vertebrate ecotoxicity	-	No	No	No	No	No	☒	☐	
Subclass 9.4 Terrestrial invertebrate ecotoxicity	-	9.4A	No	9.4B	No	9.4B	☒	☐	Classification of active based on data from formulation testing. Testing on active alone was not definitive

Table 6 Identification of cyantraniliprole

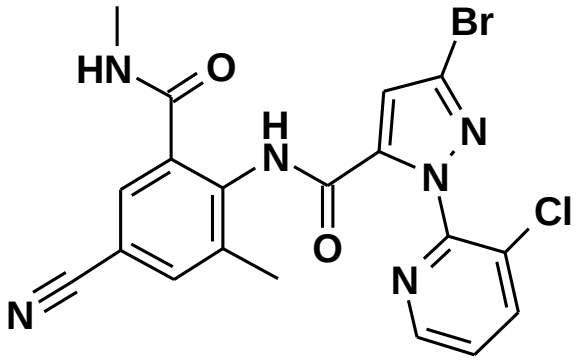
IUPAC name	3-bromo-1-(3-chloro-2-pyridyl)-4'-cyano-2'-methyl-6'-(methylcarbamoyl)pyrazole-5-carboxanilide
CAS name	3-bromo-1-(3-chloro-2-pyridinyl)-*N*-[4-cyano-2-methyl-6-[(methylamino)carbonyl]phenyl]-1*H*-pyrazole-5-carboxamide
Trade name of technical grade active	Cyazypyr™
Molecular formula	$C_{19}H_{14}BrClN_6O_2$
CAS Number	736994-63-1
Molecular weight	473.7 g/mole
Structural formula	
Purity	97% TGAI
Significant impurities/additives (% concentration)	IN-RYA13 is of potential toxicological significance – but not of concern at the specification of 0.02 g/kg. IN-Q6S09 is an impurity of toxicological significance present in the raw material IN-L8E22 – not of concern if present in IN-L8E22 at the specification of <0.001 g/kg
Other international classification & labelling	Pending

Table 7 Physical and chemical properties of the active ingredient and Benevia and Exirel

TGAI = technical grade active ingredient – PAI = pure active ingredient)

Property	Cyantraniliprole (TGAI)	Benevia	Exirel
Physical state	Solid – off-white fine powder	Liquid	Off-white liquid
Relative Density	1.38 g/mL at 20°C	0.978 g/mL at 20°C	0.982 g/mL at 20ºC
Oxidizing properties	Oxidizing properties were determined using the full train tests. The resulting burn rate of the reference standard (cellulose) was 0.851 mm/sec. None of the burn rates of any cyantraniliprole and reference standard mixtures exceeded the rate of the reference standard. Cyantraniliprole is therefore considered non-oxidizing		
pH	5.61 at 21°C 1% suspension in distilled water of cyantraniliprole TGAI	5.1 1% aqueous dispersion	5.6 1% aqueous dispersion
Explosive properties	Thermal sensitivity – negative Mechanical sensitivity - negative with respect to shock and friction	Did not react explosively to thermal stress, or mechanical stress. Thermal sensitivity – negative	Did not react explosively to thermal stress, or mechanical stress. Thermal sensitivity – negative
Henry's Law constant	Henry's Law constant in Milli-Q water at 20°C was calculated to be:		

Property	Cyantraniliprole (TGAI)	Benevia	Exirel
	1.7×10^{-13} Pa/m^3/mol 1.7×10^{-18} atm.m^3/mol (98.4% PAI)		
Melting range	217–219°C		
Vapour pressure	Estimated [EPI-Suite] 5.133×10^{-15} Pa (3.85×10^{-17} mm Hg) at 20°C 1.787×10^{-14} Pa (1.34×10^{-16} mm Hg) at 25°C (98.4% PAI)		
Viscosity	na		
Surface Tension	na	30.1 dyn/cm. (mN/m). (neat) Cyantraniliprole 100 g/L OD	25.9 ± 0.1 dyn/cm. (mN/m)
Water Solubility (mg/L)	at 20°C – 98%PAI in Milli-RO water pH 4: 17.43 ± 1.94 p pH 7: 12.33 ± 0.61 pH 9: 5.94 ± 0.61 The solubility at pH 9 has high level of uncertainty since the test substance degrades significantly over the 24 hour equilibration period		
Solvent Solubility (20°C) g/L	Acetone 6.54 ethyl acetate 1.96 dichloromethane 5.05 n-octanol 0.79		

Property	Cyantraniliprole (TGAI)	Benevia	Exirel
	methanol 4.73 n-hexane $6.7x10^{-5}$ o-xylene 0.29 acetonitrile 2.45		
Log Kow	98.4% PAI pH 4, log K_{ow}, 1.97 pH 7, log K_{ow}, 2.02 pH 9, log K_{ow}, 1.74 Lack of stability of cyantraniliprole at pH 9 caused the log K_{ow} to be lower and less reliable. There were no stability issues in reagent grade water, at pH 4 or at pH 7, and the result was nearly identical at these pHs		
Flammability	The test material melted but did not ignite, did not support combustion, and is classified as not flammable	The flash point (closed cup) of Cyantraniliprole 100 g/L OD is >99°C	The flash point (closed cup) of Cyantraniliprole 100 g/L SE is >97°C, its boiling point
Auto flammability	The test substance showed no exothermic activity up to its melting point No self-ignition (auto-flammability)	The auto-ignition temperature of the test substance = 254°C	The self-ignition temperature of Cyantraniliprole 100 g/L SE is 358°C

Mammalian toxicology - Robust study summaries for the mixture (Benevia and Exirel)[13]

Unless otherwise noted, all studies were conducted according to GLP and were fully compliant with all requirements of the standard international test methods used.

Acute toxicity (6.1) – cyantraniliprole

Acute Oral Toxicity [6.1 (oral)]

Type of Study	**Acute oral toxicity in mice – up-down procedure**
Flag	Weight of evidence
Test Substance	Cyantraniliprole tech.; batch, DPX-HGW86-23; purity, 94.5%
Endpoint	LD_{50}
Value	>5000 mg/kg b.w.
Reference	Carpenter, C. (2008a). DPX-HGW86 Technical: Acute Oral Toxicity Study in Mice - Up-and-Down Procedure. DuPont Haskell Laboratories, Newark, Delaware, USA. Laboratory Project ID: DuPont-18970. Issue date 3 April 2008. Unpublished. DuPont Report No.: DuPont-18970. US MRID 48119957 [Also CIRCA]
Klimisch Score	1
Amendments/Deviations	None
GLP	Yes
Test Guideline/s	US EPA OPPTS 870.1100 (2002); OECD 425 (2001)
Species	Mouse
Strain	Crl:CD1(ICR)
No/Group	3 Females (fasted)
Dose Levels	5000 mg/kg b.w. (20 mL/kg b.w.) [due to the body weights of 2 mice, the dose was split for these 2 mice & the second half administered after a 20 minute interval]
Exposure Type	Gavage
Analytical Measurements	Stability not determined

[13] Standard terms and abbreviations are explained in the appendix F

Study Summary	No mortalities were observed. No clinical signs of systemic toxicity were observed. There were no body weight effects noted or gross lesions present at necropsy
Additional Comments	No additional comments
Conclusion	**Cyantraniliprole requires no classification for acute oral toxicity (no marked adverse effects at the limit dose of 5,000 mg/kg b.w.), based on the submitted evidence**

Type of Study	**Acute oral toxicity in rat – up-down procedure**
Flag	Weight of evidence
Test Substance	Cyantraniliprole tech.; batch, DPX-HGW86-23; purity, 94.5%
Endpoint	LD_{50}
Value	>5000 mg/kg b.w.
Reference	Carpenter, C. (2008b). DPX-HGW86 Technical: Acute Oral Toxicity Study in Rats - Up-and-Down Procedure. DuPont Haskell Laboratories, Newark, Delaware, USA. Laboratory Project ID: DuPont-18965. Issue date 10 April 2008. Unpublished. DuPont Report No.: DuPont-18965. US MRID 48119952 [Also CIRCA]
Klimisch Score	1
Amendments/Deviations	None
GLP	Yes
Test Guideline/s	US EPA OPPTS 870.1100 (2002); OECD 425 (2001)
Species	Rat
Strain	Crl:CD(SD)
No/Group	3 Females (fasted)
Dose Levels	5000 mg/kg b.w. (20 mL/kg b.w.)
Exposure Type	Gavage
Analytical Measurements	Stability not determined
Study Summary	No mortalities were observed. No clinical signs of systemic toxicity were observed. There were no body weight effects noted or gross lesions present at necropsy

Additional Comments	No additional comments
Conclusion	**Cyantraniliprole requires no classification for acute oral toxicity (no marked adverse effects at the limit dose of 5,000 mg/kg b.w.), based on the submitted evidence**

Type of Study	**Acute oral toxicity in rat – up-down procedure**
Flag	Weight of evidence
Test Substance	DPX-HGW86-412; batch, 9182-1; purity, 97.0%
Endpoint	LD_{50}
Value	>5000 mg/kg b.w.
Reference	Carpenter, C. (2009a). Cyantraniliprole (DPX-HGW86) Technical: Acute Oral Toxicity Study in Rats - Up-and-Down Procedure. DuPont Haskell Laboratories, Newark, Delaware, USA. Laboratory Project ID: DuPont-27896. Issue date 1 June 2009. Unpublished. DuPont Report No.: DuPont-27896. US MRID 48208417 [Also CIRCA]
Klimisch Score	1
Amendments/Deviations	None
GLP	Yes
Test Guideline/s	US EPA OPPTS 870.1100 (2002); OECD 425 (2008)
Species	Rat
Strain	Crl:CD(SD)
No/Group	3 Females (fasted)
Dose Levels	5000 mg/kg b.w. (20 mL/kg b.w.)
Exposure Type	Gavage
Analytical Measurements	Stability not determined
Study Summary	No mortalities were observed. No clinical signs of systemic toxicity were observed. There were no body weight effects noted or gross lesions present at necropsy
Additional Comments	No additional comments

Conclusion	**Cyantraniliprole requires no classification for acute oral toxicity (no marked adverse effects at the limit dose of 5,000 mg/kg b.w.), based on the submitted evidence**

Type of Study	**Acute oral toxicity in rat – up-down procedure**
Flag	Weight of evidence
Test Substance	DPX-HGW86-425; batch, 9182-3B; purity, 97.7%
Endpoint	LD_{50}
Value	>5000 mg/kg b.w.
Reference	Carpenter, C. (2009b). Cyantraniliprole (DPX-HGW86) Technical: Acute Oral Toxicity Study in Rats - Up-and-Down Procedure. DuPont Haskell Laboratories, Newark, Delaware, USA. Laboratory Project ID: DuPont-27558. Issue date 11 June 2009. Unpublished. DuPont Report No.: DuPont-27558. US MRID 48208416. [Also CIRCA]
Klimisch Score	1
Amendments/Deviations	None
GLP	Yes
Test Guideline/s	US EPA OPPTS 870.1100 (2002); OECD 425 (2008)
Species	Rat
Strain	Crl:CD(SD)
No/Group	3 Females (fasted)
Dose Levels	5000 mg/kg b.w. (20 mL/kg b.w.)
Exposure Type	Gavage
Analytical Measurements	Stability not determined
Study Summary	No mortalities were observed. No clinical signs of systemic toxicity were observed. There were no body weight effects noted or gross lesions present at necropsy
Additional Comments	Different batch from Carpenter, C. (2009a)
Conclusion	**Cyantraniliprole requires no classification for acute oral toxicity (no marked adverse effects at the limit dose 5,000 mg/kg b.w.), based on the submitted evidence**

Type of Study	**Acute oral toxicity in rat – up-down procedure**
Flag	Weight of evidence
Test Substance	Cyantraniliprole tech.; batch, DPX-HGW86-648; purity, 95.6%
Endpoint	LD_{50}
Value	>5000 mg/kg b.w.
Reference	Lowe, C. (2010). Cyantraniliprole (DPX-HGW86) Technical: Acute Oral Toxicity - Up-and-Down Procedure in Rats. Eurofins PSL, Dayton, New Jersey, USA. Laboratory Project ID: EPSL Study Number: 30436. Issue date 3 November 2010. Unpublished. DuPont Report No.: DuPont-30993. US MRID 48122583. [Also CIRCA]
Klimisch Score	1
Amendments/Deviations	None
GLP	Yes
Test Guideline/s	US EPA OPPTS 870.1100 (2002); OECD 425 (2008)
Species	Rat
Strain	Crl:CD(SD)
No/Group	3 Females (fasted)
Dose Levels	5000 mg/kg b.w. (35% w/w in distilled water, 2.2-3.0 mL/animal)
Exposure Type	Gavage
Analytical Measurements	Stability not determined
Study Summary	No mortalities were observed. No clinical signs of systemic toxicity were observed. There were no body weight effects noted or gross lesions present at necropsy
Additional Comments	Different batch from Carpenter, C. (2008a,b & 2009a,b). Test substance DPX-HGW86-648 from the final commercial process
Conclusion	**Cyantraniliprole requires no classification for acute oral toxicity (no marked adverse effects at the limit dose of 5,000 mg/kg b.w.), based on the submitted evidence**

Acute Dermal Toxicity [6.1 (dermal)]

Type of Study	**Acute dermal toxicity in rats**

Flag	Key study
Test Substance	Cyantraniliprole tech.; batch, DPX-HGW86-230; purity, 94.5%
Endpoint	LD_{50}
Value	>5000 mg/kg b.w.
Reference	Carpenter, C. (2008). DPX-HGW86 Technical: Acute Dermal Toxicity Study in Rats. DuPont Haskell Laboratories, Newark, Delaware, USA. Laboratory Project ID: DuPont-18966. Issue date 1 April 2008. Unpublished. DuPont Report No.: DuPont-18966. US MRID 48119953. [Also CIRCA]
Klimisch Score	1
Amendments/Deviations	None
GLP	Yes
Test Guideline/s	U.S. EPA OPPTS 870.1200 (1998); OECD 402 (1987); EEC Method B.3. (1992)
Species	Rat
Strain	Crl:CD(SD)
No/Sex/Group	5
Dose Levels	5000 mg/kg b.w. (as a paste in 0.8 mL deionised water)
Exposure Type	Dermal, to closely shaved skin (occluded)
Analytical Measurements	Stability not determined
Study Summary	No deaths occurred. The rats exhibited no clinical signs of systemic toxicity or body weight loss. No dermal irritation was observed. No gross lesions were present in the rats at necropsy
Additional Comments	No additional comments
Conclusion	**Cyantraniliprole requires no classification for acute dermal toxicity (no marked adverse effects at the limit dose of 5,000 mg/kg b.w.), based on the submitted evidence**

Acute Inhalation Toxicity [6.1 (inhalation)]

Type of Study	**Acute inhalation toxicity in rats – nose only; single 4-hour exposure; dust aerosol**
Flag	Key study

Test Substance	Cyantraniliprole tech.; batch, DPX-HGW86-230; purity, 94.5%
Endpoint	LC_{50}
Value	>5.2 mg/L
Reference	Weinberg J.T. (2009). Acute Inhalation Toxicity Study of DPX-HGW86 Technical in Albino Rats. WIL Research Laboratories, LLC, Ashland, Ohio, USA. Study No.: WIL-189214. Issue date 12 March 2009. Unpublished. DuPont Report No.: DuPont-18971. US MRID 48119958. [Also CIRCA]
Klimisch Score	1
Amendments/Deviations	None considered significant
GLP	Yes
Test Guideline/s	US EPA OPPTS 870.1300 (1998); OECD 403 (1981); EEC Method B.2 92/69/EEC (1992)
Species	Rat
Strain	Crl:CD(SD)
No/Sex/Group	5
Dose Levels	5.2 ± 1.16 mg/L dust aerosol; MMAD (± GSD), 3.2 ± 2.18 µm
Exposure Type	Nose only
Study summary	No deaths occurred. Immediately following exposure, partial closure of the eye(s) was observed for 2 males and 3 females. There were no other toxicologically significant clinical signs immediately following exposure. The rats exhibited no clinical signs of systemic toxicity or body weight loss. No gross lesions were present in the rats at necropsy
Additional Comments	No additional comments
Conclusion	**Cyantraniliprole requires no classification for acute inhalation toxicity (no marked adverse effects at the limit concentration of 5.2 mg/L), based on the submitted evidence**

Acute toxicity (6.1) – metabolites

Acute Oral Toxicity [6.1 (oral)]

Metabolite IN-PLT97

Type of Study	**Acute oral toxicity in mice – up-down procedure**
Flag	Key study

Test Substance	IN-PLT97-003; batch, E115107-77B; purity, 98.1%
Endpoint	LD_{50}
Value	>5000 mg/kg b.w.
Reference	Carpenter, C. (2010a). IN-PLT97: Acute Oral Toxicity Study in Mice - Up-and-Down Procedure. DuPont Haskell Laboratories, Newark, Delaware, USA. Laboratory Project ID: DuPont-30571. Issue date 1 September 2010. Unpublished. DuPont Report No.: DuPont-30571. US MRID 48122579
Klimisch Score	1
Amendments/Deviations	None
GLP	Yes
Test Guideline/s	US EPA OPPTS 870.1100 (2002); OECD 425 (2008)
Species	Mouse
Strain	Crl:CD1(ICR)
No/ Group	3 Females (fasted)
Dose Levels	5000 mg/kg b.w. (20 mL/kg b.w.)
Exposure Type	Gavage
Analytical Measurements	Stability not determined
Study Summary	No deaths occurred. The mice exhibited no clinical signs or body weight losses during the study. No gross lesions were present in the mice at necropsy
Additional Comments	No additional comments
Conclusion	**Metabolite IN-PLT97 had no marked adverse effects at the limit dose of 5,000 mg/kg b.w., based on the submitted evidence**

Metabolite IN-N5M09

Type of Study	**Acute oral toxicity in mice – up-down procedure**
Flag	Key study
Test Substance	IN-N5M09-003; batch, D100855-058; purity, 99.9%
Endpoint	LD_{50}
Value	>5000 mg/kg b.w.
Reference	Carpenter, C. (2010b). IN-N5M09: Acute Oral Toxicity Study in Mice - Up-and-Down Procedure. DuPont Haskell Laboratories, Newark, Delaware, USA.

	Laboratory Project ID: DuPont-30713. Issue date 1 September 2010. Unpublished. DuPont Report No.: DuPont-30713. US MRID 48119939
Klimisch Score	1
Amendments/Deviations	None
GLP	Yes
Test Guideline/s	US EPA OPPTS 870.1100 (2002); OECD 425 (2008)
Species	Mouse
Strain	Crl:CD1(ICR)
No/ Group	3 Females (fasted)
Dose Levels	5000 mg/kg b.w. (100 mL/kg b.w. at ≤ 0.5 mL/hour)
Exposure Type	Gavage
Analytical Measurements	Stability not determined
Study Summary	No deaths occurred. The mice exhibited no clinical signs or body weight losses during the study. No gross lesions were present in the mice at necropsy
Additional Comments	No additional comments
Conclusion	**Metabolite IN-N5M09 had no marked adverse effects at the limit dose of 5,000 mg/kg b.w., based on the submitted evidence**

Metabolite IN-F6L99

Type of Study	**Acute oral toxicity in mice – up-down procedure**
Flag	Key study
Test Substance	IN-F6L99-004; purity, 98.6%
Endpoint	LD_{50}
Value	>2000 mg/kg b.w.
Reference	Finlay, C. (2006). IN-F6L99: Acute Oral Toxicity Study in Mice - Up-and-Down Procedure. DuPont Haskell Laboratories, Newark, Delaware, USA. Laboratory Project ID: DuPont-20595. Issue date 1 November 2006. Unpublished. DuPont Report No.: DuPont-20595. US MRID 46979929
Klimisch Score	1
Amendments/Deviations	None
GLP	Yes

Test Guideline/s	US EPA OPPTS 870.1100 (2002); OECD 425 (2001)
Species	Mouse
Strain	Crl:CD1(ICR)
No/ Group	3 Females (fasted)
Dose Levels	2000 mg/kg b.w.
Exposure Type	Gavage
Analytical Measurements	Stability not determined
Study Summary	No deaths occurred. The mice exhibited no clinical signs of toxicity or biologically important body weight losses after dosing. No gross lesions were present in the mice at necropsy
Additional Comments	No additional comments
Conclusion	**Metabolite IN-F6L99 had no marked adverse effects at the limit dose of 2,000 mg/kg b.w., based on the submitted evidence**

Metabolite IN-JSE76

Type of Study	**Acute oral toxicity in rats – up-down procedure**
Flag	Key study
Test Substance	IN-JSE76-005; purity, 93.8%
Endpoint	LD_{50}
Value	>5000 mg/kg b.w.
Reference	Oley, S.D. (2009). IN-JSE76: Acute Oral Toxicity - Up-and-Down Procedure in Rats. Eurofins PSL, Dayton, New Jersey, USA. Laboratory Project ID: EPSL Study No.: 26453. Issue date 12 February 2009. Unpublished. DuPont Report No.: DuPont-26932. US MRID 48119978
Klimisch Score	1
Amendments/Deviations	None
GLP	Yes
Test Guideline/s	US EPA OPPTS 870.1100 (2002); OECD 425 (2006)
Species	Rat
Strain	Sprague-Dawley derived, albino
No/ Group	3 Females (fasted)

Dose Levels	5000 mg/kg b.w. (100 mL/kg b.w. at ≤ 0.5 mL/hour)
Exposure Type	Gavage
Analytical Measurements	Stability not determined
Study Summary	All animals from each dose level survived, gained body weight, and appeared active and healthy during the study. There were no signs of gross toxicity, adverse pharmacologic effects, or abnormal behaviour No gross abnormalities were noted for any of the animals when necropsied at the conclusion of the 14-day observation period
Additional Comments	No additional comments
Conclusion	**Metabolite IN-JSE76 had no marked adverse effects at the limit dose 5,000 mg/kg b.w., based on the submitted evidence**

Skin irritation (8.2/6.3) - cyantraniliprole

Type of Study	**Acute dermal irritation in rabbits – 4-hour exposure**
Flag	Weight of evidence
Test Substance	Cyantraniliprole tech.; batch, DPX-HGW86-230; purity, 94.5%
Endpoint	Skin irritation/corrosion – Draize scores
Value	0.0 (mean of 24, 48 & 72 hour scores [Appendix 11B.2; User Guide for Thresholds and Classifications; EPA, 2012])
Reference	Carpenter, C. (2008). DPX-HGW86 Technical: Acute Dermal Irritation Study in Rabbits. DuPont Haskell Laboratories, Newark, Delaware, USA. Laboratory Project ID.: DuPont-18967. Issue date 25 March 2008. Unpublished. DuPont Report No.: DuPont-18967. US MRID 48119954. [Also CIRCA]
Klimisch Score	1
Amendments/Deviations	None
GLP	Yes
Test Guideline/s	US EPA OPPTS 870.2500 (1998); OECD 404 (2002); EEC Method B.4 (1992)
Species	Rabbit
Strain	New Zealand White
No/ Group	3 Males
Dose Levels	0.5 g

Exposure Type	As paste (in 0.4 mL deionised water) to shaved, intact skin (semi-occlusive) for 4 hours
Study Summary	No dermal irritation was observed in the rabbits. No clinical signs of toxicity were observed, and no body weight loss occurred
Additional Comments	No additional comments
Conclusion	**Cyantraniliprole requires no classification (no dermal irritation at the limit dose), based on the submitted evidence**

Type of Study	**Acute dermal irritation in rabbits – 4-hour exposure**
Flag	Weight of evidence
Test Substance	Cyantraniliprole tech.; batch, DPX-HGW86-412; purity, 97.0%
Endpoint	Skin irritation/corrosion – Draize scores
Value	0.0 (mean of 24, 48 & 72 hour scores [Appendix 11B.2; User Guide for Thresholds and Classifications; EPA, 2012])
Reference	Carpenter, C. (2009b). Cyantraniliprole (DPX-HGW86) Technical: Acute Dermal Irritation Study in Rabbits. DuPont Haskell Laboratories, Newark, Delaware, USA. Laboratory Project ID.: DuPont-27897. Issue date 21 May 2009. Unpublished. DuPont Report No.: DuPont-27897. US MRID 48208419. [Also CIRCA]
Klimisch Score	1
Amendments/Deviations	None
GLP	Yes
Test Guideline/s	US EPA OPPTS 870.2500 (1998); OECD 404 (2002); EEC Method B.4 (2004)
Species	Rabbit
Strain	New Zealand White
No/ Group	3 Males
Dose Levels	0.5 g
Exposure Type	As paste (in 0.4 mL deionised water) to shaved, intact skin (semi-occlusive) for 4 hours
Study Summary	No dermal irritation was observed in the rabbits. No clinical signs of toxicity were observed, and no body weight loss occurred

Additional Comments	Different batch
Conclusion	**Cyantraniliprole requires no classification (no dermal irritation at the limit dose), based on the submitted evidence**

Type of Study	**Acute dermal irritation in rabbits – 4-hour exposure**
Flag	Weight of evidence
Test Substance	DPX-HGW86-425; batch, 9182-3B; purity, 97.7%
Endpoint	Skin irritation/corrosion – Draize scores
Value	0.0 (mean of 24, 48 & 72 hour scores [Appendix 11B.2; User Guide for Thresholds and Classifications; EPA, 2012])
Reference	Carpenter, C. (2009a). Cyantraniliprole (DPX-HGW86) Technical: Acute Dermal Irritation Study in Rabbits. DuPont Haskell Laboratories, Newark, Delaware, USA. Laboratory Project ID: DuPont-27556. Issue date 21 May 2009. Unpublished. DuPont Report No.: DuPont-27556. US MRID 48208418. [Also CIRCA]
Klimisch Score	1
Amendments/Deviations	None
GLP	Yes
Test Guideline/s	US EPA OPPTS 870.2500 (1998); OECD 404 (2002); EEC Method B.4 (2004)
Species	Rabbit
Strain	New Zealand White
No/ Group	3 Males
Dose Levels	0.5 g
Exposure Type	As paste (in 0.4 mL deionised water) to shaved, intact skin (semi-occlusive) for 4 hours
Study Summary	No dermal irritation was observed in the rabbits. No clinical signs of toxicity were observed, and no body weight loss occurred
Additional Comments	Different batch
Conclusion	**Cyantraniliprole requires no classification (no dermal irritation at the limit dose), based on the submitted evidence**

Type of Study	**Acute dermal irritation in rabbits – 4-hour exposure**
Flag	Weight of evidence
Test Substance	Cyantraniliprole tech.; batch, DPX-HGW86-648; purity, 95.6%
Endpoint	Skin irritation/corrosion – Draize scores
Value	0.0 (mean of 24, 48 & 72 hour scores [Appendix 11B.2; User Guide for Thresholds and Classifications; EPA, 2012])
Reference	Lowe, C. (2010). Cyantraniliprole (DPX-HGW86) Technical: Primary Skin Irritation in Rabbits. Eurofins PSL, Dayton, New Jersey, USA. Laboratory Project ID: EPSL Study Number: 30438. Issue date 3 November 2010. Unpublished. DuPont Report No.: DuPont-30995. US MRID 48122584. [Also CIRCA]
Klimisch Score	1
Amendments/Deviations	None
GLP	Yes
Test Guideline/s	US EPA OPPTS 870.2500 (1998); OECD 404 (2002)
Species	Rabbit
Strain	New Zealand White
No/ Group	2 Males & 1 Female
Dose Levels	0.5 g
Exposure Type	As paste (in 0.4 mL deionised water) to shaved, intact skin (semi-occlusive) for 4 hours
Study Summary	No dermal irritation was observed in the rabbits. No clinical signs of toxicity were observed, and no body weight loss occurred
Additional Comments	Test substance DPX-HGW86-648 from the final commercial process.
Conclusion	**Cyantraniliprole requires no classification (no dermal irritation at the limit dose), based on the submitted evidence**

Eye irritation (8.3/6.4) - cyantraniliprole

Type of Study	**Acute eye irritation in rabbits – unwashed**
Flag	Weight of evidence

Test Substance	Cyantraniliprole tech.; batch, DPX-HGW86-230; purity, 94.5%
Endpoint	Eye irritation/corrosion – Draize scores
Value	0.0 for corneal opacity; 0.2 for iritis; 0.0 for conjunctival redness; 0.0 for chemosis (mean of 24, 48 & 72 hour scores [Appendix 12B.2; User Guide for Thresholds and Classifications; EPA, 2012])
Reference	Carpenter, C. (2008). DPX-HGW86 Technical: Acute Eye Irritation Study in Rabbits. DuPont Haskell Laboratories, Newark, Delaware, USA. Laboratory Project ID: DuPont-18968. Issue date 27 March 2008. Unpublished. DuPont Report No.: DuPont-18968. US MRID 48119955. [Also CIRCA]
Klimisch Score	1
Amendments/Deviations	None
GLP	Yes
Test Guideline/s	US EPA OPPTS 870.2400 (1998); OECD 405 (2002); EEC Method B.5 (1992)
Species	Rabbit
Strain	New Zealand White
No/ Group	3 Males
Dose Levels	58 mg (equivalent to 0.1 mL)
Exposure Type	Lower conjunctival sac – un-rinsed
Study Summary	At 1 hour, iritis (score of 1) was observed in the treated eye of 1 rabbit, conjunctival redness (score of 2) was observed in the treated eye of 3 rabbits, conjunctival chemosis (score of 1) was observed in the treated eye of 2 rabbits, and discharge (score of 1 or 2) was observed in the treated eye of 2 rabbits. Fluorescein stain examinations were negative for corneal injury in the treated eye of all rabbits. At 24 hours, iritis (score, 1) persisted in 1/3 rabbits No clinical signs were observed, and no body weight loss occurred in the rabbits
Additional Comments	The treated eye of 2 rabbits was normal within 24 hours, and the treated eye of the remaining rabbit was normal within 72 hours after instillation of the test substance
Conclusion	**Cyantraniliprole requires no classification (no significant eye irritation at the limit dose), based on the submitted evidence**

Type of Study	**Acute eye irritation in rabbits – unwashed**

Flag	Weight of evidence
Test Substance	DPX-HGW86-425; batch, 9182-3B; purity, 97.7%
Endpoint	Eye irritation/corrosion – Draize scores
Value	0.0 for corneal opacity; 0.0 for iritis; 0.1 for conjunctival redness; 0.0 for chemosis (mean of 24, 48 & 72 hour scores [Appendix 12B.2; User Guide for Thresholds and Classifications; EPA, 2012])
Reference	Carpenter, C. (2009a). Cyantraniliprole (DPX-HGW86) Technical: Acute Eye Irritation Study in Rabbits. DuPont Haskell Laboratories, Newark, Delaware, USA. Laboratory Project ID: DuPont-27557. Issue date 18 May 2009. Unpublished. DuPont Report No.: DuPont-27557. US MRID 48208420. [Also CIRCA]
Klimisch Score	1
Amendments/Deviations	None
GLP	Yes
Test Guideline/s	US EPA OPPTS 870.2400 (1998); OECD 405 (2002); EEC Method B.5 (1992)
Species	Rabbit
Strain	New Zealand White
No/ Group	3 Males
Dose Levels	53 mg (equivalent to 0.1 mL)
Exposure Type	Lower conjunctival sac – un-rinsed
Study Summary	Two of the rabbits pawed the treated eye after instillation of the test substance. At 1 hour the test substance produced iritis (score of 1) in 3 rabbits, conjunctival redness (score of 1 or 2) in 2 rabbits, conjunctival chemosis (score of 1) in 1 rabbit, and discharge (score of 1 or 2) in 3 rabbits. Fluorescein stain examinations of the treated eye of the rabbits were negative for corneal injury. At 24 hours, conjunctival redness persisted in 1/3 rabbits No clinical signs of toxicity were observed, and no body weight loss occurred in the rabbits
Additional Comments	The treated eye of 2 rabbits was normal within 24 hours and the treated eye of the remaining rabbit was normal within 48 hours after instillation of the test material

Conclusion	**Cyantraniliprole requires no classification, based on the submitted evidence (no significant eye irritation at the limit dose and mean Draize scores less than the specified threshold)**

Type of Study	**Acute eye irritation in rabbits – unwashed**
Flag	Weight of evidence
Test Substance	DPX-HGW86-412; batch, 9182-1; purity, 97.0%
Endpoint	Eye irritation/corrosion – Draize scores
Value	0.0 for corneal opacity; 0.0 for iritis; 0.1 for conjunctival redness; 0.0 for chemosis (mean of 24, 48 & 72 hour scores [Appendix 12B.2; User Guide for Thresholds and Classifications; EPA, 2012])
Reference	Carpenter, C. (2009b). Cyantraniliprole (DPX-HGW86) Technical: Acute Eye Irritation Study in Rabbits. DuPont Haskell Laboratories, Newark, Delaware, USA. Laboratory Project ID: DuPont-27898. Issue date 18 May 2009. Unpublished. DuPont Report No.: DuPont-27898. US MRID 48208421. [Also CIRCA]
Klimisch Score	1
Amendments/Deviations	None
GLP	Yes
Test Guideline/s	US EPA OPPTS 870.2400 (1998); OECD 405 (2002); EEC Method B.5 (2004)
Species	Rabbit
Strain	New Zealand White
No/ Group	3 Males
Dose Levels	62 mg (equivalent to 0.1 mL)
Exposure Type	Lower conjunctival sac – un-rinsed
Study Summary	At 1 hour iritis (score of 1) was observed in the treated eye of 3 rabbits, conjunctival redness (score of 1 or 2) was observed in the treated eye of 2 rabbits, conjunctival chemosis (score of 1) was observed in the treated eye of 1 rabbit, and discharge (score of 1 or 2) was observed in the treated eye of 3 rabbits. Fluorescein stain examinations of the treated eye of the rabbits were negative for corneal injury. At 24 hours, conjunctival redness persisted in 1/3 rabbits.

	No clinical signs of toxicity were observed, and no body weight loss occurred in the rabbits
Additional Comments	The treated eye of 2 rabbits was normal by 24 hours, and the treated eye of the remaining rabbit was normal by 48 hours after instillation of the test substance
Conclusion	**Cyantraniliprole requires no classification, based on the submitted evidence (no significant eye irritation at the limit dose and mean Draize scores less than the specified threshold)**

Type of Study	**Acute eye irritation in rabbits – unwashed**
Flag	Weight of evidence
Test Substance	Cyantraniliprole tech.; batch, DPX-HGW86-648; purity, 95.6%
Endpoint	Eye irritation/corrosion – Draize scores
Value	0.0 for corneal opacity; 0.0 for iritis; 0.0 for conjunctival redness; 0.0 for chemosis (mean of 24, 48 & 72 hour scores [Appendix 12B.2; User Guide for Thresholds and Classifications; EPA, 2012])
Reference	Lowe, C. (2010). Cyantraniliprole (DPX-HGW86) Technical: Primary Eye Irritation in Rabbits. Eurofins PSL, Dayton, New Jersey, USA. Laboratory Project ID: EPSL Study No.: 30437. Issue date 22 November 2010. Unpublished. DuPont Report No.: DuPont-30994. US MRID 48122585. [Also CIRCA]
Klimisch Score	1
Amendments/Deviations	None
GLP	Yes
Test Guideline/s	US EPA OPPTS 870.2400 (1998); OECD 405 (2002)
Species	Rabbit
Strain	New Zealand White
No/ Group	2 Females & 1 Male
Dose Levels	60 mg (equivalent to 0.1 mL)
Exposure Type	Lower conjunctival sac – un-rinsed
Study Summary	All animals appeared active and healthy and gained weight during the study. Apart from the eye irritation noted below, there were no other clinical signs observed.

	There was no corneal opacity or iritis noted in any treated eye during the study. At 1 hour conjunctival redness (score of 1) and discharge (scores of 1 or 2) were observed in the treated eye of all three rabbits
Additional Comments	All animals were free of ocular irritation by 24 hours. Test substance DPX-HGW86-648 from the final commercial process
Conclusion	**Cyantraniliprole requires no classification, based on the submitted evidence (no significant eye irritation at the limit dose and mean Draize scores less than the specified threshold)**

Contact sensitisation (6.5B) – cyantraniliprole

Type of Study	**Local lymph node assay (LLNA) in mice**
Flag	Weight of evidence
Test Substance	DPX-HGW86-425; batch, 9182-3B; purity, 97.7%
Endpoint	Cell proliferation in the draining auricular lymph nodes (SI)
Value	SI: 5%, 1.17; 25%, 1.24; 50%, 1.59; 70%, 1.36
Reference	Carpenter, C. (2011). Cyantraniliprole (DPX-HGW86) Technical: Local Lymph Node Assay (LLNA) in Mice. DuPont Haskell Laboratories, Newark, Delaware, USA. Laboratory Project ID: DuPont-27560, Revision No. 1. Issue date 3 March 2011. Unpublished. DuPont Report No.: DuPont-27560, Revision No. 1. US MRID 48208422. [Also CIRCA]
Klimisch Score	1
Amendments/Deviations	None
GLP	Yes
Test Guideline/s	OPPTS 870.2600 (2003); OECD Section 4 (Part 429) (2002)
Species	Mouse
Strain	CBA/JHsd
No/Sex/Group	5 Females
Dose Levels	0, 5, 25, 50 or 70% in DMF [25% hexylcinnamaldehyde in DMF as positive control]
Exposure Type	Topical to the dorsum of each ear on 3 consecutive days

Study Summary	No statistically significant differences in mean body weights and body weight gains compared to the vehicle control group were observed at any test concentration. No clinical signs of systemic toxicity were observed. Four of the 5 mice in the 25% test concentration group exhibited stained skin/fur of the ears caused by the test substance. Statistically significant increases in cell proliferation measurements compared to the vehicle control group were observed at the 50% and 70% test concentrations. However, Stimulation Indices (SIs) of less than 3.0 were observed at all test concentrations of cyantraniliprole. Therefore, the EC3 value (the estimated concentration required to induce a threshold positive response, i.e., SI = 3) for the test substance under the conditions of this study was not calculable. A 25% concentration of the positive control, HCA, produced a dermal sensitization response in mice (SI = 5.24). Therefore, the LLNA test system was valid for this study with cyantraniliprole. Under the conditions of this study, cyantraniliprole did not produce a dermal sensitization response in mice
Additional Comments	A threshold positive response requires a Stimulation Index ≥ 3
Conclusion	**Cyantraniliprole requires no classification, based on the submitted evidence (no dermal sensitisation at the concentrations tested, max. 70%)**

Type of Study	**Local lymph node assay (LLNA) in mice**
Flag	Weight of evidence
Test Substance	Cyantraniliprole tech.; batch, DPX-HGW86-230; purity, 94.5%
Endpoint	Cell proliferation in the draining auricular lymph nodes (SI)
Value	SI: 5%, 1.13; 25%, 1.12; 50%, 1.70; 100%, 1.35
Reference	Hoban, D. (2007). DPX-HGW86: Local Lymph Node Assay (LLNA) in Mice. DuPont Haskell Laboratories, Newark, Delaware, USA. Laboratory Project ID: DuPont-18969. Issue date 6 November 2007. Unpublished. DuPont Report No.: DuPont-18969. US MRID 48119956. [Also CIRCA]
Klimisch Score	1
Amendments/Deviations	None
GLP	Yes
Test Guideline/s	US EPA OPPTS 870.2600 (2003); OECD 429 (2001)
Species	Mouse

Strain	CBA/JHsd
No/Sex/Group	5 Females
Dose Levels	0, 5, 25, 50 or 100% (1 g/mL) in DMF [25% hexylcinnamaldehyde in DMF as positive control]
Exposure Type	Topical to the dorsum of each ear on 3 consecutive days
Study Summary	No statistically significant differences in mean body weights and body weight gains compared to the vehicle control group were observed at any test concentration. A statistically significant increase in mean body weight gains compared to the vehicle control group was observed in the positive control group. No clinical signs of systemic toxicity were observed. No statistically significant increases in cell proliferation measurements compared to the vehicle control group were observed at any test concentration. Stimulation indices (SIs) of less than 3.0 were observed at all test concentrations of DPX-HGW86. Therefore, the EC3 value (the estimated concentration required to induce a threshold positive response, i.e., SI = 3) for the test substance under the conditions of this study was not calculable. A 25% concentration of the positive control, HCA, produced a dermal sensitization response in mice (SI = 7.95). Therefore, the LLNA test system was valid for this study with DPX-HGW86. Under the conditions of this study, DPX-HGW86 did not produce a dermal sensitization response in mice
Additional Comments	A threshold positive response requires a Stimulation Index ≥ 3
Conclusion	**Cyantraniliprole requires no classification, based on the submitted evidence (no dermal sensitisation at the concentrations tested, max. 100%)**

Type of Study	**Local lymph node assay (LLNA) in mice**
Flag	Weight of evidence
Test Substance	DPX-HGW86-412; batch, 9182-1; purity, 97.0%
Endpoint	Cell proliferation in the draining auricular lymph nodes (SI)
Value	SI: 5%, 1.11; 25%, 0.69; 50%, 0.92; 70%, 0.94
Reference	Hoban, D. (2009). Cyantraniliprole (DPX HGW86) Technical: Local Lymph Node Assay (LLNA) in Mice. DuPont Haskell Laboratories, Newark, Delaware, USA. Laboratory Project ID: DuPont-27899. Issue date 14 April 2009. Unpublished. DuPont Report No.: DuPont-27899. US MRID 48208423. [Also CIRCA]
Klimisch Score	1
Amendments/Deviations	None
GLP	Yes
Test Guideline/s	US EPA OPPTS 870.2600 (2003); OECD 429 (2002)
Species	Mouse
Strain	CBA/JHsd
No/Sex/Group	5 Females
Dose Levels	0, 5, 25, 50 or 70% in DMF [25% hexylcinnamaldehyde in DMF as positive control]
Exposure Type	Topical to the dorsum of each ear on 3 consecutive days
Study Summary	No statistically significant differences in mean body weights and body weight gains compared to the vehicle control group were observed at any test concentration. No clinical signs of systemic toxicity were observed at any concentration. No statistically significant increases in cell proliferation measurements compared to the vehicle control group were observed at any test concentration. Stimulation indices (SIs) of less than 3.0 were observed at all test concentrations of cyantraniliprole. Therefore, the EC3 value (the estimated concentration required to induce a threshold positive response, i.e., SI = 3) for the test substance under the conditions of this study was not calculable. A 25% concentration of the positive control, HCA, produced a dermal sensitization response in mice (SI = 7.99). Therefore, the LLNA test system was valid for this

	study with cyantraniliprole. Under the conditions of this study, cyantraniliprole did not produce a dermal sensitization response in mice
Additional Comments	A threshold positive response requires a Stimulation Index ≥ 3
Conclusion	**Cyantraniliprole requires no classification, based on the submitted evidence (no dermal sensitisation at the concentrations tested, max. 100%)**

Type of Study	**Dermal sensitisation – modified Buehler Method**
Flag	Weight of evidence
Test Substance	Cyantraniliprole tech.; batch, DPX-HGW86-648; purity, 95.6%
Endpoint	Dermal sensitisation – Draize scores after challenge
Value	Erythema: 0.23 at 24 & 0.10 at 48 hours (mean scores)
Reference	Lowe, C. (2010). Cyantraniliprole (DPX-HGW86) Technical: Dermal Sensitisation Test - Buehler Method. Eurofins PSL, Dayton, New Jersey, USA. Laboratory Project ID: EPSL Study No.: 30439. Issue date 3 November 2010. Unpublished. DuPont Report No.: DuPont-30418. US MRID 48122586. [Also CIRCA]
Klimisch Score	1
Amendments/Deviations	None
GLP	Yes
Test Guideline/s	US EPA OPPTS 870.2600 (2003); OECD 406 (1992)
Species	Guinea pig
Strain	Hartley albino
No/Sex/Group	20 Males
Dose Levels	Epicutaneous induction: 0.4 g at 55% w/w; challenge: 0.4 g at 55% w/w in mineral oil [alpha-hexylcinnamaldehyde as positive control]
Exposure Type	Topical 6-hour induction exposure on 3 consecutive weeks; topical challenge 27 days after first induction exposure
Study Summary	Very faint erythema (0.5) was noted for six test sites at various intervals during the induction phase. In the challenge phase, very faint erythema (0.5) was noted for nine of twenty test sites 24 hours after the challenge application.

	The percentage of sensitisation at 24 and/or 48 hours for the test article animals challenged with 55% of test substance was 0%. No responses were noted in the vehicle control naive animals. Historical control data using HCA demonstrated a positive response and was conducted within the guideline-required 6-month timeframe from initiation of the study with cyantraniliprole No test substance-related clinical signs of toxicity were observed. There were no test substance-related body weight effects noted
Additional Comments	Study conducted with test substance DPX-HGW86-648 from the final commercial process
Conclusion	**Cyantraniliprole requires no classification, based on the submitted evidence (no dermal sensitisation at the concentrations tested, max. 55%)**

Type of Study	**Dermal sensitisation – Maximisation Test**
Flag	Weight of evidence
Test Substance	Cyantraniliprole tech.; batch, DPX-HGW86-648; purity, 95.6%
Endpoint	Dermal sensitisation – Magnusson & Kligman's criteria
Value	Negative
Reference	Nomura, N. (2011). A Skin Sensitisation Study of DPX-HGW86 Technical in Guinea Pigs (Maximization Test). Kannami Laboratory, Bozo Research Center Inc., Tagata-gun, Shizuoka, Japan. Study No.: I-3659. Issue date 7 April 2011 (Revision 1). Unpublished. DuPont Report No.: DuPont-30996, Revision No. 1. US MRID 48122599. [Also CIRCA]
Klimisch Score	1
Amendments/Deviations	None significant
GLP	Yes
Test Guideline/s	OECD 406 (1992)
Species	Guinea pig
Strain	Hartley albino
No/Sex/Group	20 Females
Dose Levels	Intradermal induction: 5 or 10% as a 1:1 emulsion of water & Freund's Complete Adjuvant (FCA); epicutaneous induction: 50% ; challenge: 50% in liquid paraffin [1-chloro-2,4-dinitrobenzene (DNCB) as the positive control]

Exposure Type	Intradermal induction followed approx. 1 week later with topical 48-hour induction exposure; topical challenge 2 weeks later
Study Summary	No skin reaction was observed during the challenge phase. The percentage of sensitisation at 24 and/or 48 hours for the test article animals challenged with 0.1 mL of test substance at 50% was 0%. A dermal sensitisation response was noted in 100% of the animals treated with a 0.1% DNCB in olive oil for the historical positive control. No responses were noted in the vehicle or positive control vehicle animals No clinical signs of toxicity were observed. There were no body weight effects noted
Additional Comments	Test substance DPX-HGW86-648 from the final commercial process
Conclusion	**Cyantraniliprole requires no classification, based on the submitted evidence (no dermal sensitisation at the concentrations tested, max. 50%)**

Type of Study	**Dermal sensitisation – Maximisation Test**
Flag	Weight of evidence
Test Substance	Cyantraniliprole tech.; batch, DPX-HGW86-230; purity, 94.5%
Endpoint	Dermal sensitisation – Magnusson & Kligman's criteria
Value	Positive
Reference	Oley, S.D. (2010). Cyantraniliprole (DPX-HGW86) Technical: Dermal Sensitisation – Magnusson-Kligman Maximization Method. Eurofins, Product Safety Laboratories, Dayton, New Jersey, USA. Laboratory Project ID: EPSL Study No.: 28166. Issue date 9 February 2010. Unpublished. DuPont Report No.: DuPont-29062. US MRID 48119984. [Also CIRCA]
Klimisch Score	1
Amendments/Deviations	None
GLP	Yes
Test Guideline/s	US EPA OPPTS 870.2600 (2003); OECD 406 (1992)
Species	Guinea pig
Strain	Hartley albino
No/Sex/Group	20 Males

Dose Levels	Intradermal induction: 5% w/w in propylene glycol with FCA; epicutaneous induction: 0.5 g at 75% w/w in propylene glycol; challenge: 0.5 mL of 56% or 19% w/w in propylene glycol
Exposure Type	Intradermal induction followed 6 days later with topical 6-hour induction exposure; topical challenge 2 weeks later
Study Summary	All test and vehicle control animals survived, appeared active and healthy during the study and gained body weight over the entire study. Following the challenge phase, the overall body weight gain of the test substance group was statistically decreased by 85% compared to the test substance vehicle control animals. During the induction phase, faint erythema (score of 1) was noted for most test sites 24 and 48 hours after intradermal injections of an emulsion of FCA (50% v/v in distilled water). Very faint erythema (score of 0.5) was evident at one site at 24 hours. Animals receiving injections of a 5% w/w mixture of test substance in propylene glycol showed very faint erythema (score of 0.5) on some test sites after 24 and/or 48 hours. Animals receiving injections of a 5% w/w mixture of the test substance in an emulsion of Freund's Adjuvant Complete (50% v/v in distilled water) showed very faint to faint erythema (scores of 0.5 to 1) for all test sites after 24 and 48 hours. During the topical induction phase very faint to faint erythema (scores of 0.5 to 1) was noted for all test sites one hour after patch removal. Nineteen of twenty test animals challenged with the highest non-irritating concentration (HNIC; 56% w/w) showed faint to moderate erythema (scores of 1 to 2) 24 hours after challenge patch removal. The responses persisted at eighteen sites through 48 hours with very faint erythema (score of 0.5) present at all other sites. Seventeen of twenty animals challenged with 33% dilution of HNIC (19% w/w) showed faint erythema (score of 1) 24 hours after patch removal. The responses persisted at six sites through 48 hours with very faint erythema (score of 0.5) present at most other sites. Appropriate historical control data using alpha-hexylcinnamaldehyde technical (HCA) demonstrated a positive response
Additional Comments	Test substance DPX-HGW86-230 is stated to have been synthesised by an early pre-commercial process that has subsequently been abandoned
Conclusion	**The synthesis route used for DPX-HGW86-230 produces material with the potential to cause dermal sensitisation (at the concentrations tested), based on the submitted evidence**

General conclusion about acute toxicity

Cyantraniliprole (DPX-HGW86) was shown to have low acute toxicity by the oral (4 batches), dermal and inhalation routes. Cyantraniliprole was shown to be non-irritating to the skin and to the eye (both with 4 batches). The synthesis route used for cyantraniliprole batch DPX-HGW86-230 produces material with the potential to cause dermal sensitisation. However other batches were shown not be potential contact sensitisers in the LLNA, and cyantraniliprole from the final commercial process, DPX-HGW86-648, was shown not to be a potential contact sensitiser in the modified Buehler Method (DuPont-30418; MRID 48122586) and Maximisation Test (DuPont-30996; MRID 4812259).

Metabolites IN-PLT97, IN-N5M09, IN-F6L99 and IN-JSE76 were shown to have low acute toxicity by the oral route (no adverse effects at the limit doses used), based on the submitted evidence.

Genotoxicity (6.6)

In Vitro Studies – Cyantraniliprole

Study type/Test Guideline	Result	Reference
Bacterial Reverse Mutation Assay [US EPA OPPTS 870.5100 (1998), ECC 2000/32/EC, Annex 4D-B13/14 No., L136 (2000), OECD No. 471 (1998)]	Negative (± S9)	Wagner, V.O. VanDyke, M.R. (2010); Cyantraniliprole (DPX-HGW86) technical: Bacterial reverse mutation assay, DuPont-30991. BioReliance, Rockville, Maryland, USA Report No.: AD10PN.503.BTL. MRID 48122587. [Also CIRCA]. [Test substance: DPX-HGW86-648; batch, D100487-104; purity, 95.6%]
Bacterial Reverse Mutation Assay [US EPA OPPTS 870.5100 (1998), ECC 2000/32/EC, Annex 4D-B13/14 No., L136 (2000), OECD No. 471 (1998)]	Negative (± S9)	Wagner, V.O. VanDyke, M.R. (2009a); Cyantraniliprole (DPX-HGW86) technical: Bacterial reverse mutation assay, DuPont-27160. BioReliance, Rockville, Maryland, USA Report No.: AC25MV.503.BTL. MRID 48119980. [Also CIRCA]. [Test substance: DPX-HGW86-425; batch, 9182-3B; purity, 97.7%]
Bacterial Reverse Mutation Assay [US EPA OPPTS 870.5100 (1998), ECC 2000/32/EC, Annex 4D-B13/14 No., L136 (2000), OECD No. 471 (1998)]	Negative (± S9)	Wagner, V.O. VanDyke, M.R. (2009b); Cyantraniliprole (DPX-HGW86) technical: Bacterial reverse mutation assay, DuPont-27900. BioReliance, Rockville, Maryland, USA Report No.: AC25SL.503.BTL. MRID 48208424. [Also CIRCA]. [Test substance: DPX-HGW86-412; batch, 9182-1; purity, 97.0%]

Mammalian Chromosome Aberration Test [US EPA OPPTS 870.5375 (1998), ECC 2000/32/EC, Annex 4A-B10 No., L136 (2000), OECD No. 473 (1998)]	Negative (± S9)	Gudi, R., Rao, M. (2009a); Cyantraniliprole (DPX-HGW86) technical: *In vitro* mammalian chromosome aberration test. DuPont-27901; BioReliance, Rockville, Maryland, USA, Report No.: AC25SL.341.BTL (MRID 48208426). [Also CIRCA]. [Test substance: DPX-HGW86-412; batch, 9182-1; purity, 97.0%]
Mammalian Chromosome Aberration Test [US EPA OPPTS 870.5375 (1998), ECC 2000/32/EC, Annex 4A-B10 No., L136 (2000), OECD No. 473 (1998)]	Negative (± S9)	Gudi, R., Rao, M. (2009b); Cyantraniliprole (DPX-HGW86) technical: *In vitro* mammalian chromosome aberration test. DuPont-27559; BioReliance, Rockville, Maryland, USA, Report No.: AC25MV.341.BTL (MRID 48208425). [Also CIRCA]. [Test substance: DPX-HGW86-425; batch, 9182-3B; purity, 97.7%]
Mammalian Chromosome Aberration Test [US EPA OPPTS 870.5375 (1998), ECC 2000/32/EC, Annex 4A-B10 No., L136 (2000), OECD No. 473 (1998)]	Negative (± S9)	Madraymootoo, W., Jois, M. (2010); Cyantraniliprole (DPX-HGW86) technical: *In vitro* mammalian chromosome aberration test. DuPont-30990; BioReliance, Rockville, Maryland, USA, Report No.: AD10PN.341.BTL (MRID 48122588). [Also CIRCA]. [Test substance: DPX-HGW86-648; batch, D100487-104; purity, 95.6%]
Mammalian Gene Mutation Assay [US EPA OPPTS OPPTS 5300 (1998); ECC 2000/32/EC, Annex 4E No., L136 (2000); OECD 476 (1997)]	Negative (± S9)	Clarke, J.J. (2010); Cyantraniliprole (DPX-HGW86) technical: In vitro mammalian cell gene mutation test (CHO/HGPRT) assay. DuPont-30992; BioReliance, Rockville, MD, Report No.: AD10PN.782.BTL (MRID 48122589). [Also CIRCA]. [Test substance: DPX-HGW86-648; batch, D100487-104; purity, 95.6%]
Mammalian Gene Mutation Assay [US EPA OPPTS OPPTS 5300 (1998); ECC 2000/32/EC, Annex 4E No., L136 (2000); OECD 476 (1997)]	Negative (± S9)	Stankowski, L.F. (2011); Cyantraniliprole (DPX-HGW86) technical: CHO/HPRT forward mutation assay with duplicate cultures. DuPont-31372; Covance Laboratories, Inc., Vienna, Virginia, USA Report No.: 8236883 (MRID 48208443). [Also CIRCA]. [Test substance: DPX-HGW86-412; batch, 9182-1; purity, 97.0%]
Conclusion		**Cyantraniliprole (DPX-HGW86), in three different batches, was shown not to have**

		genotoxic potential in *in vitro* test systems, based on the submitted evidence

In Vivo Studies – Cyantraniliprole

Type of Study	**Micronucleus Test – mouse bone marrow**
Flag	Key study
Test Substance	DPX-HGW86-412; batch, 9182-1; purity, 97.0%
Endpoint	Micronucleated polychromatic erythrocytes (MNPCE) frequency
Value	Negative
Reference	Donner, E.M. (2011); Cyantraniliprole (DPX-HGW86) technical: Mouse bone marrow micronucleus test. DuPont Haskell Laboratories, Newark, DE; DuPont-31373. (MRID 48208444). [Also CIRCA]
Klimisch Score	1
Amendments/Deviations	None
GLP	Yes
Test Guideline/s	US EPA OPPTS 870.5395 (1998); ECC 2000/32/EC, Annex 4C-B12 No., L136 (2000); OECD 474 (1998)
Species	Mouse
Strain	Crl:CD1(ICR)
No/Sex/Group	10 for control, low- & intermediate dose groups; 14 for high-dose groups
Dose Levels	0, 500, 1000 or 2000 mg/kg b.w.
Study Summary	In the main study, no clinical signs of toxicity or mortality were observed at any dose levels tested in male and female mice exposed to the test substance. No abnormalities were detected in the vehicle or positive control groups. There were no significant changes in body weight or body weight gain in either male or female animals administered the test substance. No statistically significant increases in micronucleated polychromatic erythrocyte (PCE) frequency were observed in any evaluated test substance-treated group of male or female animals at the 24-hour time point, or in female animals at the highest dose level at the 48-hour time-point. A statistically significant increase observed at the highest dose level in male animals at the 48-hour time-point was considered spurious, within laboratory historical control range, and without biological relevance.

	There were no test substance–related statistically significant decreases in PCEs among 1000 erythrocytes. The positive control groups exhibited a response consistent with the micronucleated PCE historical control data
Additional Comments	Statistically significant increases in MNPCE frequency were found in CP-treated (positive control) animals of both sexes
Conclusion	**Cyantraniliprole (DPX-HGW86) was shown not to have genotoxic potential in this *in vivo* test system, based on the submitted evidence**

In Vitro Studies – metabolites

Metabolite IN-JSE76

Study type/Test Guideline	**Result**	**Reference**
Bacterial Reverse Mutation Assay [US EPA OPPTS 870.5100 (1998), ECC 2000/32/EC, Annex 4D-B13/14 No., L136 (2000), OECD No. 471 (1998)]	Negative (± S9)	Wagner, V.O., VanDyke, M.R. (2009a); IN-JSE76: Bacterial reverse mutation assay. BioReliance, Rockville, Maryland, USA. Testing Laboratory Report No.: AC22CC.503.BTL. DuPont Report No.: DuPont-24716. Study Completion Date: February 25, 2009. MRID Unpublished. [Also CIRCA]. [Test substance: IN-JSE76; batch, 005; purity, 93.8%]
Mammalian Chromosome Aberration Test [US EPA OPPTS 870.5375 (1998), ECC 2000/32/EC, Annex 4A-B10 No., L136 (2000), OECD No. 473 (1998)]	Negative (± S9)	Gudi, R., Rao, M. (2010); IN-JSE76: *In vitro* mammalian chromosome aberration test. BioReliance, Rockville, Maryland, USA. Testing Laboratory Report No.: AC22CC.341.BTL. DuPont Report No.: DuPont-24715, Revision No. 2. Study Completion Date: January 30, 2009. Revised Report Completion Date: July 07, 2009. Second Revised Report Completion Date: March 12, 2010. MRID 48119975. Unpublished. [Also CIRCA]. [Test substance: IN-JSE76; batch, 005; purity, 93.8%]
Mammalian Gene Mutation Assay [US EPA OPPTS OPPTS 5300 (1998); ECC 2000/32/EC, Annex 4E No., L136 (2000); OECD 476 (1997)]	Negative (± S9)	Clarke, J.J. (2009); IN-JSE76: *In vitro* mammalian cell gene mutation test (CHO/HGPRT Assay). BioReliance, Rockville, Maryland, USA. Testing Laboratory Report No.: AC22CC.782.BTL. DuPont Report No.: DuPont-24714. Study Completion Date: February 04, 2009. MRID

		48119974. Unpublished. [Also CIRCA]. [Test substance: IN-JSE76; batch, 005; purity, 93.8%]

Metabolite IN-PLT97

Study type/Test Guideline	Result	Reference
Bacterial Reverse Mutation Assay [US EPA OPPTS 870.5100 (1998), ECC 2000/32/EC, Annex 4D-B13/14 No., L136 (2000), OECD No. 471 (1998)]	Negative (± S9)	Wagner, V.O., Jois, M. (2010); IN-PLT97: Bacterial reverse mutation assay. BioReliance, Rockville, Maryland, USA. Testing Laboratory Report No.: AD08NK.503.BTL. DuPont Report No.: DuPont-30552, Revision No.1. Study completion date: October 08, 2010, Amended Final Report Date: October 20, 2010. MRID 48122580. Unpublished. [Also CIRCA]. [Test substance: IN-PLT97-003; batch, E115107-77B; purity, 98.1%]
Mammalian Chromosome Aberration Test [US EPA OPPTS 870.5375 (1998), ECC 2000/32/EC, Annex 4A-B10 No., L136 (2000), OECD No. 473 (1998)]	Negative (± S9)	Madraymootoo, W., Jois, M. (2011); IN-PLT97: *In vitro* mammalian chromosome aberration test. BioReliance, Rockville, Maryland, USA. Testing Laboratory Report No.: AD08NK.341.BTL. DuPont Report No.: DuPont-30551, Revision No. 1. MRID 48122581. Study completion date: October 29, 2010. Revised final date: April 12, 2011. Unpublished. [Also CIRCA]. [Test substance: IN-PLT97-003; batch, E115107-77B; purity, 98.1%]
Mammalian Gene Mutation Assay [US EPA OPPTS OPPTS 5300 (1998); ECC 2000/32/EC, Annex 4E No., L136 (2000); OECD 476 (1997)]	Negative (± S9)	Clarke, J.J. (2010); IN-PLT97: *In vitro* mammalian cell gene mutation test (CHO/HGPRT Assay). BioReliance, Rockville, Maryland, USA. Testing Laboratory Report No.: AD08NK.782.BTL. DuPont Report No.: DuPont-30365. November 10, 2010. MRID 48122582. Unpublished. [Also CIRCA]. [Test substance: IN-PLT97-003; batch, E115107-77B; purity, 98.1%]

Metabolite IN-F6L99

Study type/Test Guideline	Result	Reference

Bacterial Reverse Mutation Assay [US EPA OPPTS 870.5100 (1998), ECC 2000/32/EC, Annex 4D-B13/14 No., L136 (2000), OECD No. 471 (1998)]	Negative (± S9)	Myhre, A. (2006); IN-F6L99: Bacterial reverse mutation test. DuPont Haskell Laboratories, Newark, Delaware, USA. Testing Laboratory Report No. DuPont-20597. November 15, 2006. MRID 4697993. Unpublished. [Also CIRCA]. [Test substance: IN-F6L99; batch, 003; purity, 98.6%]

Metabolite IN-N5M09

Study type/Test Guideline	Result	Reference
Bacterial Reverse Mutation Assay [US EPA OPPTS 870.5100 (1998), ECC 2000/32/EC, Annex 4D-B13/14 No., L136 (2000), OECD No. 471 (1998)]	Negative (± S9)	Wagner III, V.O., VanDyke, M.R. (2009b); IN-N5M09: Bacterial reverse mutation assay. BioReliance, Rockville, Maryland, USA. Laboratory Report No.: AC29WT.503.BTL. DuPont Report No. DuPont-28800. September 24, 2009. MRID 48119982. Unpublished. [Also CIRCA]. [Test substance: IN-N5M09-003; batch, D100855-058; purity, 99.9%]

General conclusion about genotoxicity

Cyantraniliprole (DPX-HGW86) was shown not to have genotoxic potential in *in vitro* and *in vivo* test systems, based on the submitted evidence, and does not require classification as a mutagen.

Metabolites IN-JSE76, IN-PLT97, IN-F6L99 and IN-N5M09 were shown not to have genotoxic potential in *in vitro* test systems, based on the submitted evidence.

Carcinogenicity (6.7)

Type of Study	**Combined chronic toxicity / oncogenicity study – 2-year feeding in rats**	
Flag	Weight of evidence	
Test Substance	Cyantraniliprole tech.; batch, DPX-HGW86-41; purity, 97.0%	
Endpoints	Non-Neoplastic Effects	LOAEL: 2000 ppm (males: 84.8 mg/kg b.w./day; females: 106.6 mg/kg b.w./day), based on histopathological changes in the liver (males and females)
		NOAEL: 200 ppm (males: 8.3 mg/kg/b.w./day; females: 10.5 mg/kg b.w./day)
	Neoplastic Effects	LOAEL: >20,000 ppm

		NOAEL: 20,000 ppm (males: 906.6 mg/kg b.w./day; females: 1160.8 mg/kg b.w./day)
Tumours	See Table B (below)	
Malignant/Benign	See Table B (below)	
Background Incidence	Not applicable	
Time of Onset	Not applicable	
Survival	Not affected	
Reference	Craig, L. (2011); Cyantraniliprole technical (DPX-HGW86 commercial batch - 412): Combined chronic toxicity/oncogenicity study 2-year feeding study in rats. MPI Research, Inc., Mattawan, Michigan, USA. Unpublished laboratory report No. 125-101. DuPont-26842. April/28/ 2011. MRID 48122577. [Also CIRCA]	
Klimisch Score	1	
Amendments/Deviations	None significant	
GLP	Yes	
Test Guideline/s	US EPA OPPTS 870.4300 (1998); OECD Section 4 (Part 453) (1981 and 2009); Commission Directive 88/302/EC Part B.33 (1988)	
Species	Rat	
Strain	Crl:CD(SD)	
No/Sex/Group	70 (10 per group for 12-month chronic toxicity study)	
Dose Levels	0, 20, 200, 2,000 or 20,000 ppm [mean intakes, males: 0, 0.8, 8.3, 84.8, & 906.6 mg/kg b.w./day; females: 0. 1.1, 10.5, 106.6, 1160.8 mg/kg b.w./day]	
Exposure Type	Diet	
Study Summary	Exposure to 20,000 ppm produced small reductions in body weight, body weight gain, and food efficiency, primarily over the first 1-1.5 years of dietary exposure. Mean body weight at 20,000 ppm was 6% and 9% below control in males and females, respectively, at Week 52, and was 6% and 4% below control values in males and females, respectively (not statistically significant) at termination. Mean body weight gain in this group was 8% and 15% below control in males and females, respectively, over Weeks 2 to 52. Over the two year period, mean body weight gain was 8% and 7% less than control values in males and females, respectively (not statistically significant). There was no test article-related effect on food consumption in either sex. The reduced body weight gain was associated with lower mean food efficiency over the first year at 20,000 ppm. Overall (2-year) food efficiency was comparable to controls. No adverse effects on body weight or nutritional parameters were observed in any other dose group. Mean body weight was lower in females at 2000 ppm over most of the first year of the study and body weight gain was significantly below control over the first 13 weeks of the study, but not over the entire first year. This finding, although likely to be test article-related, was considered non-	

adverse, based on the small magnitude of the difference and the fact that the animals recovered over the remainder of the study.

No test article-related effects were noted on cause of death, macroscopic findings, or in the incidence of masses.

No test article-related effects were noted in clinical pathology parameters at <2000 ppm. At the 12-month interval a few male animals at 20,000 ppm exhibited moderate increases in GGT (gamma glutamyltransferase), AST (aspartate aminotransferase), ALT (alanine aminotransferase), and sorbitol dehydrogenase relative to expected ranges. This collection of changes was considered test article-related and correlates to the histopathologic changes in the liver.

Following the one year interim, test article-related increased mean liver weights occurred in both male and female rats at 2000 and 20,000 ppm (Table A). At the terminal necropsy liver weights were only statistically significantly increased in the 20,000 ppm males. The increased liver weights correlated to hepatocellular hypertrophy noted in both sexes following the interim and terminal necropsies. Hepatocellular hypertrophy was also noted in females at 2000 ppm. This change was likely to be the result of enzyme induction and was not considered adverse. There was no test article-related increase in the incidence of tumours.

Following two years of exposure to the test article, there was an increase in the incidence of foci of cellular alteration (clear, eosinophilic, and basophilic) and focal vacuolation (morphologically compatible with focal fatty change) at 20,000 ppm in male livers. At 2000 ppm, clear cell foci of cellular alteration and focal vacuolation were also increased, and there was a non-statistically significant increase in eosinophilic foci (Table A).

At termination, there was an increase in incidence and a very minimal increase in severity of chronic progressive nephropathy in the kidneys in females at 20,000 ppm. Chronic progressive nephropathy was stated to be a common finding in aged rodents as reflected by the high incidence in the concurrent controls, and the current finding did not show a dose-related response. These two observations support the determination that the chronic progressive nephropathy seen in treated rats was not compound-related

Table A. Incidences of non-neoplastic microscopic pathology [CIRCA MRID 48122577]

ppm	0	20	200	2000	20000
Males:					
12-month					
Liver, centrilobular hypertrophy	0/10	0/10	0/10	5/10	8/10
24-month					
Liver, centrilobular hypertrophy	0/60	0/60	0/60	0/60	6/60#*
Liver focus of cellular alteration, clear	0/60	0/60	1/60	4/60#	5/60#
Liver focus of cellular alteration, eosinophilic	20/60	15/60	12/60	29/60	32/60#*

Liver focus of cellular alteration, basophilic	10/60	9/60	9/60	12/60	20/60[#]
Liver vacuolation, focal	4/60	4/60	7/60	13/60[#*]	13/60[#*]
Females:					
12-month					
Liver, centrilobular hypertrophy	0/10	0/10	0/10	4/10	6/10
Liver, panlobular hypertrophy	0/10	0/10	0/10	0/10	1/10
24-month					
Liver, centrilobular hypertrophy	0/60	0/60	0/60	9/60[#*]	22/60[#*]
Kidney, nephropathy, chronic progressive	34/60	37/60	32/60	44/60	45/60[#]

[#] Significantly different from control by Cochran-Armitage trend test p <0.05.

* Significantly different from control by Fisher's exact test, p <0.05.

Note: Statistical analyses were not conducted on the microscopic findings at one year.

In males, there was an increase in the incidence of combined pancreas islet cell adenoma/carcinoma in 20 ppm (17%), 2000 ppm (22%), and 20,000ppm (13%) relative to the controls (7%), and at 200 ppm the incidence was the same as the controls (Table B). With Fisher's Exact Test, the increase of combined adenomas/carcinomas at 2000 ppm showed a statistical difference from the controls (p<0.05). At 20,000 ppm, no statistical significance was demonstrated. An increase in liver adenomas was seen in the 20,000 ppm males but the increase did not demonstrate a statistical significance, and there was no dose-related response.

In females, there was a slight increase in the incidence of thyroid follicular cell adenomas/ carcinomas in 2000 and 20,000ppm groups. The increase at 20,000 ppm showed a significant trend only. This increase was not significant by the Fisher's exact test (p = 0.4958), was not associated with statistically significant increases in follicular cell adenomas or combined follicular cell adenoma/carcinoma, and was within the range of historical control for this tumour type in female rats at this laboratory (0-3.3%). In addition, there was no increase in follicular cell adenomas or carcinomas in male rats at any concentration tested. The male rat is stated to be more sensitive to xenobiotic-induced proliferative lesions of thyroid follicular cells than the female rat.

It was concluded that the pancreas islet cell tumour and liver tumour in males and thyroid follicular cell tumour in females were not treatment related for the following reasons: (1) the increase did not demonstrate a dose-related response, (2) no consistent statistical significant difference existed between the control and the treated groups, and (3) the increase was slight over a broad range of dosing concentrations.

Table B. Incidences of neoplastic microscopic pathology [CIRCA MRID 48122577]

ppm	0	20	200	2000	20000
Male					
Pancreas, islet cell					
Adenomas	2/60	3/48	3/44	4/40	5/60
Carcinomas	2/60	5/48	0/44	5/40	3/60
adenoma/ carcinoma	4/60 (7%)	8/48 (17%)	3/44 (7%)	9/40[#] (22%)	8/60 (13%)

Liver					
Adenomas	1/60	2/60	1/60	2/60	4/60
Carcinomas	2/60	0/60	0/60	1/60	2/60
Adenomas/carcinomas	3/60	2/60	1/60	3/60	6/60
Female					
Thyroid gland					
Adenoma, follicular cell	1/60	3/60	1/60	1/59	2/60
Carcinoma, follicular	0/60	0/60	0/60	2/59	2/60
Adenoma/ carcinoma	1/60	3/60	1/60	3/59	4/60*

*: Statistically significant by the Cochran-Armitage trend test, p <0.05. # Statistically significant by the Fisher's exact test, p <0.05

Data excerpted from 2062-2088 of the report.

Additional Comments	No additional comments
Conclusion	**Cyantraniliprole did not produce compound-related or dose-related increases in tumour incidence in rats, based on the evidence submitted**

Type of Study	**Oncogenicity study – 18-month feeding in mice**	
Flag	Weight of evidence	
Test Substance	Cyantraniliprole tech.; batch, DPX-HGW86-41; purity, 97.0%	
Endpoints	Non-Neoplastic Effects	LOAEL: >7,000 ppm
		NOAEL: 7000 ppm (768.8 & 903.8 mg/kg b.w./day in males and females, respectively; highest concentration tested)
	Neoplastic Effects	LOAEL: >7,000 ppm
		NOAEL: 7,000 ppm
Tumours	Not applicable	
Malignant/Benign	Not applicable	
Background Incidence	Not applicable	
Time of Onset	Not applicable	
Survival	Not applicable	

Reference	Craig, L. (2011); Cyantraniliprole (DPX-HGW86) technical: Oncogenicity study 18-month feeding study in mice. MPI Research, Inc., Mattawan, Michigan, USA. Laboratory Report No.: 125-100. DuPont-26843. April 26, 2011. MRID 48122578. Unpublished. [Also CIRCA]
Klimisch Score	1
Amendments/Deviations	None significant
GLP	Yes
Test Guideline/s	US EPA OPPTS 870.4200 (1998); OECD Section 4 (Part 451) (1981 and 2009); Commission Directive 88/302/EC Part B.32 (1988)
Species	Mouse
Strain	Crl:CD1(ICR)
No/Sex/Group	60
Dose Levels	0, 20, 150, 1000 or 7,000 ppm [mean intakes, males: 0, 2, 15.5, 103.6 & 768.8 mg/kg b.w./day; females: 0. 2.4, 18.6, 131.0 & 903.8 mg/kg b.w./day]
Exposure Type	Diet
Study Summary	There were no test article-related effects on survival, or increases in the incidence of clinical or ophthalmological observations or masses over the course of this study. No differences in clinical pathology parameters (WBC differential counts or blood cell morphology) were observed Minor test article-related differences in body weight and nutritional parameters were noted during the study at 7000 ppm. Due to the small magnitude of these changes and resolution during the treatment period, these reductions were not considered adverse A test article-related increase in liver weights was observed in males and females at ≥ 1000 ppm. Increased liver weights correlated with the microscopic finding of hepatocellular hypertrophy at these levels in both sexes. The liver weight increase and microscopic correlate were consistent with pharmacological induction of hepatic enzymes and interpreted to not be adverse. There were no test article-related macroscopic or other microscopic findings. There was no test article-related neoplasia in this study
Additional Comments	No additional comments
Conclusion	**Cyantraniliprole did not produce compound-related or dose-related increases in tumour incidence in mice, based on the evidence submitted**

General conclusion about carcinogenicity

Cyantraniliprole did not produce compound-related or dose-related increases in tumour incidence in rats or mice, based on the evidence submitted.

Reproductive/developmental toxicity (6.8)

Developmental Toxicity

Type of Study	**Developmental Study – gavage, rats**	
Flag	Weight of evidence	
Test Substance	DPX-HGW86-230; batch, HGW86-0603-1; purity, 94.5%	
Endpoints	Parental Toxicity	LOAEL: >1000 mg/kg b.w./day
		NOAEL: 1000 mg/kg b.w./day
	Foetal Toxicity	LOAEL: >1000 mg/kg b.w./day
		NOAEL: 1000 mg/kg b.w./day
Reference	Munley, S.M. (2009a); DPX-HGW86 technical: Developmental toxicity in rats. DuPont Haskell Laboratories, Newark, Delaware, USA. Testing Facility Report No. DuPont-19188. April 17, 2009. MRID 48119968. Unpublished. [Also CIRCA]	
Klimisch Score	1	
Amendments/Deviations	None	
GLP	Yes	
Test Guideline/s	US EPA OPPTS 870.3700 (1998); OECD 414 (2001); Directive 87/302/EEC Part B	
Species	Rat	
Strain	Crl:CD(SD)	
No/ Group	22	
Dose Levels	0, 20, 100, 300 or 1000 mg/kg b.w./day on Gestation Days 6-20	
Exposure Type	Gavage	
Study Summary	There were no early deaths; all animals on study survived until scheduled euthanasia.	

	There were no test substance-related clinical observations at any dose level tested; with the exception of a single female from the 300 mg/kg b.w./day group with hair loss, all animals appeared normal throughout the study No test substance-related effects on body weight, weight gain or food consumption were observed at any dose level There were no test substance-related maternal gross observations at any dose level tested; with the exception of a single female from the 20 mg/kg b.w./day group with a small placenta, all animals appeared normal at necropsy There were no test substance-related effects on any reproductive outcome or litter data endpoint. Group mean data for the numbers of *corpora lutea*, implantations, resorptions, live and dead foetuses, sex ratio, and foetal weight were comparable across all groups tested There were no test substance-related foetal malformations or variations at any dose level tested. Data collected during the foetal external, visceral, head, and skeletal exams were generally comparable across all groups tested
Additional Comments	Test substance DPX-HGW86-230 was synthesised by an early pre-commercial process that has subsequently been abandoned
Conclusion	**Cyantraniliprole (batch DPX-HGW86-230) did not show any specific adverse effects on developmental parameters in rats, based on the evidence submitted**

Type of Study	**Developmental Study – gavage, rabbits**	
Flag	Weight of evidence	
Test Substance	DPX-HGW86-230; batch, HGW86-0603-1; purity, 94.5%	
Endpoints	Parental Toxicity	LOAEL: 100 mg/kg b.w./day (based on ↓ food consumption and body weight losses)
		NOAEL: 25 mg/kg b.w./day
	Foetal Toxicity	LOAEL: 250 mg/kg b.w./day (↓ mean foetal b.w.)
		NOAEL: 100 mg/kg b.w./day
Reference	Munley, S.M. (2009b); DPX-HGW86 technical: Developmental toxicity study in rabbits. DuPont Haskell Laboratories, Newark, Delaware, USA. Testing Facility Report No. DuPont-19189. July 12, 2009. MRID 48119969. Unpublished. [Also CIRCA]	
Klimisch Score	1	

Amendments/Deviations	None
GLP	Yes
Test Guideline/s	US EPA OPPTS 870.3700 (1998); OECD 414 (2001); Directive 87/302/EEC Part B
Species	Rabbit
Strain	Hra:(NZW)SPF
No/ Group	22
Dose Levels	0, 25, 100, 250 or 500 mg/kg b.w./day on Gestation Days 7-28
Exposure Type	Gavage
Study Summary	At 100 mg/kg b.w./day, two does were sacrificed early (gestation days [GD] 15 and 24) following prolonged periods of markedly reduced food consumption and body weight losses At 250 and 500 mg/kg b.w./day, there was a low incidence of increased abortions and/or deliveries between GD 22 and 29 that resulted in the sacrifice of four and three does at these doses, respectively, prior to scheduled termination. All but one female at 250 mg/kg b.w./day was observed with diarrhoea and/or reduced or absent faeces prior to signs of abortion. In general, those females that aborted or delivered on the day of scheduled termination had prolonged periods of markedly reduced food consumption and subsequent body weight losses that preceded the abortion/early delivery. Based on these marked reductions in body weight and food consumption as well as the clinical observations consistent with the reduced food consumption, these late gestation abortions were considered secondary to the overt indications of adverse maternal toxicity in these does Body weight gains that were lower or statistically significantly lower than controls were evident after about a week of dosing resulting in overall body weight gains calculated over GD 7 to 29 that were 35%, 78%, and 75% lower than control at 100, 250, and 500 mg/kg b.w./day, respectively. Maternal body weight changes using the final body weight adjusted for the weight of the gravid uterus also reflected greater losses when compared with the control group; during GD 7 to 29, does lost an average of 181, 291, and 267 grams at 100, 250, and 500 mg/kg b.w./day, respectively, compared with an average loss of 107 and 88 grams at 0 and 25 mg/kg b.w./day Test substance-related effects on maternal food consumption were observed at 100 mg/kg b.w./day and above. Reductions in mean food consumption were evident after the first few days of dosing and persisted for the duration of the

	study, and statistically significant reductions in group means were observed on many occasions during the study at 250 mg/kg b.w./day and above. Overall food consumption means calculated from gestation day 7 to 29 were approximately 9%, 20%, and 20% lower than the control group mean at 100, 250, and 500 mg/kg b.w./day, respectively No test substance-related gross lesions were observed at necropsy. At 25 mg/kg b.w./day, one female had a discoloured spleen; since this was observed in a single animal, it was not considered test substance-related. At 100 mg/kg b.w./day, two females that were sacrificed early due to weight loss and markedly reduced food consumption were observed with empty intestines. At 250 and 500 mg/kg b.w./day, there were observations in one or two animals involving the abdominal viscera and included empty intestines and discoloured organs; these observations were most frequently observed in animals that had either aborted or delivered early Effects on reproductive outcome data were limited to test substance-related, statistically significant reductions in mean foetal weight at 250 and 500 mg/kg b.w./day. Mean foetal weights were 10 and 8% lower than the control group mean at 250 and 500 mg/kg b.w./day, respectively. Mean foetal weights at 25 and 100 mg/kg b.w./day were within 1% of the control group mean. Otherwise, data for the mean numbers of implantations, resorptions, live and dead foetuses, and litter sex ratio were comparable across all groups tested There were no test substance-related foetal malformations or variations observed at any dose level tested during the external, head, visceral, and skeletal examinations. The alterations that were reported were not remarkable, occurred with low frequency, and without any evidence of a dose response
Additional Comments	Test substance DPX-HGW86-230 was synthesised by an early pre-commercial process that has subsequently been abandoned
Conclusion	**Cyantraniliprole (batch DPX-HGW86-230) did not show any specific adverse effects on developmental parameters in rabbits up to doses causing significant maternal toxicity, based on the evidence submitted**

Reproductive toxicity

Type of Study	**2-Generation Reproduction study – diet, rats**
Flag	Key study
Test Substance	DPX-HGW86-230; batch, HGW86-0603-1; purity, 94.5%

Endpoints	Parental Toxicity	LOAEL: 200 ppm (14 mg/kg b.w./day) (based on thyroid follicular epithelial cell hypertrophy)
		NOAEL: 20 ppm (1.4 mg/kg b.w./day)
	Reproductive Toxicity	LOAEL: >20000 ppm
		NOAEL: 20000 ppm (1344 mg/kg b.w./day)
	Offspring Toxicity	LOAEL: 2000 ppm (136 mg/kg b.w./day) (based on decreased thymus and spleen weights)
		NOAEL: 200 ppm
Reference	Barnett, J.F., Jr. (2011); DPX-HGW86 technical: Oral (diet) two-generation (one litter per generation) reproduction toxicity study in rats. Charles River Laboratories, Horsham, Pennsylvania, U.S.A. Report No.: AUV00033. DuPont-19187. April 21, 2011. MRID 48119967. Unpublished. [Also CIRCA]	
Klimisch Score	1	
Amendments/Deviations	None	
GLP	Yes	
Test Guideline/s	US EPA OPPTS 870.3800 (1998); OECD No. 416 (2001)	
Species	Rat	
Strain	Crl:CD(SD)	
No/Sex/Group	30	
Dose Levels	0, 20, 200, 2000 or 20,000 ppm [mean intakes (premating P_1 females): 0, 1.4, 13.9, 136 & 1343.6 mg/kg b.w./day]	
Exposure Type	Diet	
Study Summary	*Parents* Under the conditions of the study, cyantraniliprole produced treatment-related effects on the parental animals at dietary concentrations of 200, 2000 and 20,000 ppm. For the parental animals, reductions in body weight and body weight gains at 20,000 ppm P_1 and F_1 generation male and female rats were found (absolute body weight:↓4% - ↓11%; body weight gains: ↓5% -↓20%). There was an increased incidence and severity of cytoplasmic vacuolation of the cells of the adrenal cortex in all treated P_1 males (14/30, 13/30, 17/30 & 10/10) and in the females at 200, 2000 and 20,000 ppm (16/30, 24/30 & 9/10). In the controls the incidence was 3/10 for males and 2/10 for females. In the males this vacuolation occurred mostly in the zona fasciculata, while fine	

vacuolation was observed in the cells of the zona glomerulosa in females. Whilst treatment-related, the toxicological significance of these observations in the adrenals is unclear in the absence of clear histopathology or dysfunction

In the liver, treatment-related minimal or mild centrilobular hepatocellular hypertrophy was noted in P_1 males (25/30 & 9/10) and females (17/30 & 9/11), and F_1 males (12/30 & 7/10) and females (5/30 & 6/10) at 2000 and 20,000 ppm. The hepatocellular hypertrophy was characterised by enlarged centrilobular hepatocytes with increased amounts of pale eosinophilic “ground glass” cytoplasm, and margination of basophilic stippling in the cytoplasm. The hepatocellular change was more often discernible in the subcapsular lobules.

A significant increase in the fixed thyroid lobes/parathyroid weights (absolute and relative) was seen in the 20,000 ppm P_1 and F_1 males and in 200, 2000, and 20,000 ppm P_1 and F_1 females. A corresponding dose-related increase in the incidence of the thyroid follicular epithelial cell hypertrophy/hyperplasia was found in the 2000 and 20,000 ppm P_1 males (16/30 & 9/10) and in 200, 2000, and 20,000 ppm P_1 females (18/30, 24/30 & 9/10). In the controls the incidence was 3/10 in males, and 4/10 in females. The hyperplasia was typified by increases in follicular epithelial cells, and the hypertrophy by a taller epithelium with an increase in smaller follicles. In the F_1 generation an increased incidence &/or severity (mild to moderate) of the thyroid follicular epithelial cell hypertrophy/hyperplasia was noted in 2000 and 20,000 ppm males (16/30 & 9/10) and 20,000 ppm females (9/10). In the controls the incidence was 4/10 in males, and 5/10 in females. In addition, significant reductions in thymus weight accompanied by thymus atrophy were noted in 2000 and 20,000 ppm P_1 female rats (thymus weight: ↓22% - ↓28%). Thymus weight in 20,000 ppm F_1 females was also decreased (↓33%)

Reproduction

There was no adverse, test substance-related reproductive toxicity at any level tested in this study up to 20,000 ppm. Data describing gonadal structure and function, including oestrous cyclicity and sperm analyses, mating behaviour, conception and fertility, partuition, gestation length, lactation, weaning and the growth and development of offspring including onset of puberty were all comparable across the exposure groups tested. Any test substance-related effects that occurred for any of these endpoints were all considered secondary to test substance-related effects on body weight parameters

Offspring

For the offspring, treatment-related effects included decreased body weights at 20,000 ppm in the F_1 generation pups on PNDs 15 and 22 (↓11% - ↓14%), and

	in F_2 generation pups from birth to PND 22 (↓10% - ↓15%.). Pup thymus and spleen weights were decreased in 20000 ppm F_1 males and in 2000 and 20,000 ppm F_2 males and females (↓19% - ↓26%). Decreases in 20,000 ppm F_1 and F_2 pup brain weight and F_2 pup adrenal weight were also found. An increase in the number of 20,000 ppm F_1 pups with dehydration was also seen
Additional Comments	Test substance DPX-HGW86-230 was synthesised by an early pre-commercial process that has subsequently been abandoned The study authors considered that the significant increase in the fixed thyroid lobes/parathyroid weights (absolute and relative) seen in the 200 ppm P_1 and F_1 females was not adverse, as the change was not correlated with microscopic evidence of thyroid follicular cell hypertrophy. As this correlation was noted at 2000 & 20,000 ppm, the change was considered adverse at these dose levels. However, the pathology report does note an increased incidence and severity of hypertrophy and hyperplasia of the thyroid follicular epithelial cells in P_1 females at 200 ppm (18/30; 11 minimal, 7 mild; *cf* control: 4/10; 2 minimal, 2 mild). The type of change in the thyroid was noted as often encountered in association with hepatocellular hypertrophy occurring with compounds producing enzyme induction in rats. [Histopathology Report, Page 981-998 of 2303] The CIRCA review gave 200 ppm as the parental LOAEL, based on the thyroid endpoint, while noting the changes at 2000 ppm were more conclusive
Conclusion	**Cyantraniliprole (batch DPX-HGW86-230) did not show any specific adverse effects on reproduction parameters in rats, based on the evidence submitted**

General conclusion about developmental and reproductive toxicity

Cyantraniliprole (batch DPX-HGW86-230) did not show any specific adverse effects on developmental or reproduction parameters in rats or rabbits, based on the evidence submitted.

Target organ systemic toxicity (6.9)

Type of Study	**Sub acute inhalation toxicity – 4 weeks, rats**
Flag	Weight of evidence
Test Substance	Cyantraniliprole tech.; batch, DPX-HGW86-586; purity, 95.6%%
Endpoint	LOAEL: None identified

<table>
<tr><td></td><td>NOAEL: females: 100 mg/m^3 (highest concentration tested); males: 100 mg/m^3 (highest concentration tested)</td></tr>
<tr><td>Reference</td><td>Ng SP (2011); Cyantraniliprole (DPX-HGW86) Technical: Four-Week inhalation Toxicity Study in Rats. DuPont Haskell Global Centers for Health & Environmental Sciences, Newark, Delaware 19714, USA. Laboratory Report No.: DuPont-32967. November 18, 2011. MRID 48119945. Unpublished. [Also CIRCA].</td></tr>
<tr><td>Klimisch Score</td><td>1</td></tr>
<tr><td>Amendments/Deviations</td><td>None</td></tr>
<tr><td>GLP</td><td>Yes</td></tr>
<tr><td>Test Guideline/s</td><td>OECD 412; Commission Directive 92/69/EEC Part B.8 (1992)</td></tr>
<tr><td>Species</td><td>Rat</td></tr>
<tr><td>Strain</td><td>Crl:CD(SD)</td></tr>
<tr><td>No/Sex/Group</td><td>20/sex for controls and top dose groups, and 10/sex for the two mid dose groups, in order to provide 10 control and 10 top dose animals for a 2 week recovery period.</td></tr>
<tr><td>Dose Levels</td><td>0, 10, 100 mg/m^3 over a 4 week period (a total of 21 exposures).
Nose-only exposure, 6 hours/day, 5 days/week.
The analyses of the aerosols were as follows:
<table>
<tr><th>Target concentration</th><th>Gravimetric concentration</th><th>Mass Median Aerodynamic Diameter (MMAD) [geometric standard deviation]</th></tr>
<tr><td>1 mg/m^3</td><td>1.4mg/m^3 ±0.13 mg/m^3</td><td>2.9 µm [GSD = 2.3]</td></tr>
<tr><td>10 mg/m^3</td><td>11 mg/m^3 ±0.53 mg/m^3</td><td>2.5 µm [GSD = 2.4]</td></tr>
<tr><td>100 mg/m^3</td><td>100 mg/m^3 ±1.0 mg/m^3</td><td>3.0 µm [GSD = 2.3]</td></tr>
</table></td></tr>
<tr><td>Study Summary</td><td>Exposure to cyantraniliprole did not produce any test substance-related changes in body weights, body weight gains, daily food consumption, daily food efficiency or ophthalmological observations and no clinical signs of toxicity were observed over the course of the study.
There were no adverse changes in clinical pathology. One day after the final exposure top dose animals showed reductions in serum bilirubin, but this difference did not persist in the recovery group and was not considered adverse.</td></tr>
</table>

	Exposure-related focal squamous metaplasia of the larynx was seen in 8/10 males in the 100 mg/m^3 group. This finding was reversible. Minimal squamous metaplasia was seen in 1/10 female animals in the 100 mg/m^3 recovery group which was considered by researchers to be a spurious finding. There were no test substances- related organ weight changes or gross observations in this study. The study authors consider the NOAEL to be the top dose, 100 mg/m^3
Additional Comments	If the laryngeal pathology is considered substance-related and adverse, then the substance would trigger classification as 6.9B (although the duration is 4 weeks). Staff note the references cited in support of the minor toxicological significance of the laryngeal findings (Osimitz, T.G. et al.; 2007)
Conclusion	Under the conditions of this study, cyantraniliprole did not demonstrate, based on the evidence submitted, that it should be classified 6.9B for repeated inhalation dose Target Organ Systemic Toxicity (Table 17.2; User Guide for Thresholds and Classifications; EPA, 2012)

Type of Study	**Subchronic Toxicity – 90-day feeding, rats**
Flag	Weight of evidence
Test Substance	Cyantraniliprole tech.; batch, DPX-HGW86-141; purity, 93.4%
Endpoint	LOAEL: females: 400 ppm (27 mg/kg b.w./day); males: 20,000 ppm (1147 mg/kg b.w./day) (based on thyroid follicular cell hypertrophy)
	NOAEL: females: 100 ppm (7 mg/kg b.w./day); males: 3000 ppm (168 mg/kg b.w./day)
Reference	Carpenter, C. (2007); DPX-HGW86 technical: Subchronic toxicity 90-day feeding study in rats. DuPont Haskell Laboratories, Newark, Delaware, USA. Laboratory Report No.: DuPont-16993. July 23, 2007. MRID 48119945. Unpublished. Gannon, S.A. (2011b); DPX-HGW86 technical: Subchronic toxicity 90-day feeding study in rats. DuPont Haskell Laboratories, Newark, Delaware, USA. Laboratory Report No.: DuPont-16993, Supplement No.1, Revision No. 1. 48119946. April 16, 2011. MRID 48119946. Unpublished (analysis of blood samples for metabolites). [Also CIRCA]
Klimisch Score	1
Amendments/Deviations	None

GLP	Yes
Test Guideline/s	US EPA OPPTS 870.3100 (1998); OECD 408 (1998); Commission Directive 2001/59/EC Part B.26 (2001)
Species	Rats
Strain	Crl:CD(SD)
No/Sex/Group	10 (plus 5 in satellite groups terminated on Days 29/30)
Dose Levels	0, 100, 400, 3000 or 20,000 ppm [mean intakes, males: 0, 6, 22, 168 & 1147 mg/kg b.w./day; females: 0, 7, 27, 202 & 1346 mg/kg b.w./day]
Study Summary	Under the conditions of this study cyantraniliprole did not produce test substance-related deaths, clinical signs, ophthalmological observations, changes on body weights or nutritional parameters, clinical pathology parameters (haematology, clinical chemistry, coagulation parameters, urinalysis), or gross pathology in treated male and female rats Increases in liver weight were observed in males ≥3000 ppm at 28 days and ≥400 ppm at 90 days. In females, liver weights were increased at ≥400 ppm at both 28 and 90 days. The increases in liver weight were accompanied by centrilobular hepatocellular hypertrophy observed in male (≥3000 ppm) and female (≥400 ppm) 90-day animals and in female (≥3000 ppm) 28-day animals. Similarly, total hepatic cytochrome P-450 content was increased in males at the 28-day (20,000 ppm) and 90-day (3000 and 20,000 ppm) time-points and in females at the 90-day time-point (20,000 ppm). The effects on the liver were considered by the authors to be an adaptive response Mean relative and absolute thyroid weights were increased (variable statistical significance) in the 28-day sacrifice 20,000 ppm female group. No adverse effects were observed on organ weights in male 28-day sacrifice rats or on gross or microscopic parameters in male or female 28-day sacrifice rats Thyroid follicular cell hypertrophy was observed in 90-day males fed 20,000 ppm and in 90-day females fed 400, 3000 or 20,000 ppm and was regarded as adverse. The thyroid hypertrophy correlated with alterations in thyroid hormone concentrations and induction of UDP-glucuronyltransferase activity and, in females, increased mean thyroid weights at these dietary levels. Alterations in thyroid hormone concentrations were also observed in male rats at 400 and 3000 ppm, but were not considered adverse as there was no correlative histopathology or alterations in UDP-glucuronyltransferase activity. A minimal to mild increase in adrenal cortical microvesiculation in male rats in the 90-day

	sacrifice 20,000 ppm males was considered to be a non-adverse change within normal physiological limits The results of the supplemental study (Gannon, S.A., 2011b) showed that the most abundant analyte present in the plasma of male and female rats was IN-MLA84 followed by parent cyantraniliprole and IN-J9Z38. Concentrations were higher in females than males at all dietary concentrations, except for IN-J9Z38, and the plasma concentrations approached a plateau above a dietary concentration of 400 ppm
Additional Comments	No additional comments
Conclusion	**Under the conditions of this study, cyantraniliprole (batch DPX-HGW86-141) induced adverse effects in the thyroid of rats, with the females being most sensitive (LOAEL: 27 mg/kg b.w./day). Cyantraniliprole should be classified 6.9B for repeated oral dose Target Organ Systemic Toxicity (Table 17.2; User Guide for Thresholds and Classifications; EPA, 2012), based on the evidence submitted**

Type of Study	**Subchronic Toxicity – 90-day feeding, mice**
Flag	Weight of evidence
Test Substance	Cyantraniliprole tech.; batch, DPX-HGW86-141; purity, 93.4%
Endpoint	LOAEL: 7000 ppm (males: 1092 mg/kg b.w./day; females: 1344 mg/kg b.w./day) based on increased incidence of focal necrosis of the liver and increases in liver weight.
	NOAEL: 1000 ppm (males: 150 mg/kg b.w./day; females: 204 mg/kg b.w./day). *NB: NOAEL/LOAEL revised following secondary CIRCA review – see additional comment below.*
Reference	MacKenzie, S.A. (2007); DPX-HGW86 technical: Subchronic toxicity 90-day feeding study in mice. DuPont Haskell Laboratories, Experimental Pathology Laboratories, Inc., Newark, Delaware, USA, Sterling, Virginia, USA. Laboratory Report No.: DuPont-16992. April 17, 2007. MRID 48119943 Gannon, S.A. (2011a); DPX-HGW86 technical: Subchronic toxicity 90-day feeding study in mice. DuPont Haskell Laboratories, Newark, Delaware, USA. Laboratory Report No.: DuPont-16992, Supplement No.1, Revision No. 1. April 6, 2011. MRID 48119944. Unpublished. (analysis of blood samples for metabolites). [Also CIRCA]
Klimisch Score	1

Amendments/Deviations	None
GLP	Yes
Test Guideline/s	US EPA OPPTS 870.3100 (1998); OECD 408 (1998); Commission Directive 2001/59/EC Part B.26 (2001)
Species	Mice
Strain	Crl:CD1(ICR)
No/Sex/Group	10 (plus 5 in satellite groups dosed for 63 days)
Dose Levels	0, 50, 300, 1000 or 7000 ppm [mean intakes, males: 0, 7, 47, 150 & 1092 mg/kg b.w./day; females: 0, 10, 58, 204 & 1344 mg/kg b.w./day]
Study Summary	No test substance-related deaths occurred, and no clinical or ophthalmological observations were attributed to exposure to the test substance No test substance-related effects on any body weight or nutritional parameters were observed There were no treatment-related changes in clinical pathology parameters (haematology and plasma total protein) In males exposed to dietary concentrations of 7000 ppm of the test substance, mean absolute and mean relative (% body weight) liver weights were increased 24% and 26%, respectively, as compared to control values. These increases were both statistically significant. In females, mean absolute liver weights were increased 7% and 15% in the 1000 and 7000 ppm groups, respectively. Mean relative liver weights were increased 11% and 24% in the 1000 and 7000 ppm groups, respectively. Only the mean relative liver weight increases were statistically significant The increased liver weights correlated with microscopic hepatocellular hypertrophy at the same concentration levels. Both the liver weight increases and the hepatocellular hypertrophy were considered indicative of non-adverse hepatic enzyme induction. Centrilobular hepatocellular hypertrophy was observed in both males and females and the incidence and severity were dose related. In males, hypertrophy was present in 0/10, 0/10, 0/10, 0/10 and 2/10 mice at 0, 50, 300, 1000 and 7000 ppm, respectively, and both were graded as minimal (grade 1 of 4). In females, hepatocellular hypertrophy was present in 0/10, 0/10, 0/10, 1/10 and 9/10 mice at 0, 50, 300, 1000 and 7000 ppm, respectively. All were graded as minimal, except for six (6/9) 7000 ppm females, which were graded mild (grade 2 of 4). The hepatocellular hypertrophy was characterized by an increase in the size of centrilobular hepatocytes due to an increase in cytoplasmic volume.

	A minimal to mild increase in microvesiculation of the zona fasciculata cells of the adrenal cortex was observed in 0/10, 3/10, 5/10, 4/10, and 7/10 males at 0, 50, 300, 1000, and 7000 ppm, respectively. Twelve (12/19) were graded as minimal (grade 1 of 4) and 7 (7/19) were graded as mild (grade 2 of 4). Increased microvesiculation was characterized by a diffuse increase (beyond that observed in about 90% of untreated mice) in the amount of small lipid vacuoles within the zona fasciculata of the cortex. In this study, the incidence did not exhibit a monotonic dose response, and the severity of increased microvesiculation was not dose related. Nonetheless, the incidence in all exposed groups was greater than the control incidence. Although a spuriously lower control group incidence is possible, it was considered most likely that the increased microvesiculation was test substance-related at all concentrations Increased microvesiculation of the adrenal gland cortex was not observed in females. However, since female mouse adrenal cortices are normally highly microvesiculated, resembling the mild (grade 2 of 4) increased microvesiculation in males, small differences would probably not be detected. The minimal to mild increase in adrenal cortical microvesiculation in males was considered to be a non-adverse change within normal physiological limits. [Adrenal cortical cells in the zona fasciculata synthesize and store corticosteroids as regulated by adrenocorticotropin (ACTH) from the pituitary. Adrenal cortical microvesiculation is the normal morphological expression of cytoplasmic corticosteroid lipid accumulation. Since the adrenal cortical microvesiculation observed in all mice in this study was within the range of normal adrenal morphology and there was no evidence of adrenal cellular degeneration or toxicity, the test substance-related (males only) minimal to mild increase in microvesiculation was interpreted to be non-adverse.] The results of the supplemental study (Gannon, S.A., 2011a) showed that IN-MLA84 was the most prevalent analyte present in male or female mice, followed by cyantraniliprole. Plasma values for all the evaluated metabolites were similar between males and females at comparable diet concentrations
Additional Comments	Following secondary review, the CIRCA evaluation revised the NOAEL from 7000 ppm to to 1000 ppm, with the LOAEL established as 7000 ppm. This was based on an increased incidence of focal necrosis of the liver and increases in liver weight
Conclusion	**Under the conditions of this study, cyantraniliprole (batch DPX-HGW86-141) induced adverse effects on the liver in mice at 7000 ppm (1092/1344 mg/kg b.w./day for males/females). The LOAEL is outside the guidance value ranges (Table 17.2; User Guide for Thresholds and Classifications;**

	EPA, 2012) and so cyantraniliprole should not be classified under 6.9B for repeated oral dose Target Organ Systemic Toxicity, based on the evidence submitted

Type of Study	**Subchronic Toxicity – 90-day feeding, dog**
Flag	Weight of evidence
Test Substance	Cyantraniliprole tech.; batch, DPX-HGW86-141; purity, 93.4% [Test facility analysis: 92.2%]
Endpoint	LOAEL: 1000 ppm (males: 32 mg/kg b.w./day; females: 34 mg/kg b.w./day) (based on changes in clinical chemistry liver markers)
	NOAEL: 100 ppm (males/females: 3 mg/kg b.w./day)
Reference	Luckette, E.M. (2007); DPX-HGW86 technical: 90-day dietary toxicity study in dogs. MPI Research, Mattawan, Michigan, USA. Laboratory Report No**.:** 125-055. DuPont -16994, Revision No. 1. August 29, 2007. MRID 48119948. Unpublished Gannon, S.A. (2009); DPX-HGW86 Technical: 90-day dietary toxicity study in dogs. MPI Research, Mattawan, Michigan, USA. Laboratory Report No.: 125-055. DuPont-16994, Supplement No.1, Revision No. 1. November 26, 2007. MRID 48119947. Unpublished. (This supplemental report provides information on analytical results for cyantraniliprole and its metabolites in the plasma samples collected from the 90-day toxicity study in dogs). [Also CIRCA]
Klimisch Score	1
Amendments/Deviations	None
GLP	Yes
Test Guideline/s	US EPA OPPTS 870.3150; OECD 409
Species	Dog
Strain	Beagle
No/Sex/Group	4
Dose Levels	0, 30, 100, 1000 or 10,000 ppm [mean intakes, males: 0, 1, 3, 32 & 281 mg/kg b.w./day; females: 0, 1, 3, 34 & 294 mg/kg b.w./day]
Study Summary	One male dog in the 10,000 ppm group (animal number 133) was found dead on Day 52. The cause of death was not determined but may have been secondary to canine juvenile polyarteritis syndrome (CJPS), and not a direct

	effect of test article exposure. All other animals survived until their scheduled termination. A few 10,000 ppm dogs with microscopic pathology suggestive of CJPS demonstrated clinical signs attributed to this condition. These dogs were also noted to be thin, which correlated with lower body weight Adverse, test article-related reductions in body weight, body weight gain, food consumption, and food efficiency were observed in male and female dogs in the 10,000 ppm group. Males were more severely affected than females. No adverse effects on any of these parameters were observed in male or female dogs at 1000 ppm or below Adverse, test article-related changes in clinical chemistry were observed in ≥1000 ppm dogs (decreased total protein and albumin concentrations) and 10,000 ppm dogs (increased alanine aminotransferase activity, decreased glucose, decreased cholesterol. No adverse test article-related effects were observed in haematology, coagulation, or urinalysis parameters in any group and no adverse test article-related effects on any clinical pathology parameter were observed at ≤100 ppm A test article-related increase in liver weights was observed at 100 ppm and above but was considered non-adverse in the absence of correlative microscopic changes. Minimal bile duct hyperplasia was observed in male and female dogs at 10,000 ppm and was considered test article related and adverse. Three dogs (two males, one female) at 10,000 ppm had microscopic pathology of the coronary and other arteries, and secondary effects in the myocardium. These effects were attributed to CJPS and not to direct effects of test article exposure. However, exposure to 10,000 ppm DPX-HGW86 may have exacerbated this condition The results of the supplemental study (Gannon, S.A., 2009) showed that the most abundant analyte in plasma was parent cyantraniliprole, which was present at comparable concentrations in both males and females at the same dietary concentrations. The concentration of other metabolites examined (IN-J9Z38, IN-MYX98, IN-MLA84, and IN-N7B69) was essentially negligible relative to that of the parent compound. The concentration of each analyte was not linear with dose
Additional Comments	No additional comments
Conclusion	**Under the conditions of this study, cyantraniliprole (batch DPX-HGW86-141) induced adverse effects in the liver of dogs (LOAEL: 32 & 34 mg/kg b.w./day in males and females, respectively). Cyantraniliprole should be classified 6.9B for repeated oral dose Target Organ Systemic Toxicity**

	(Table 17.2; User Guide for Thresholds and Classifications; EPA, 2012), based on the evidence submitted

Type of Study	**Chronic Toxicity – 1-year feeding, dog**
Flag	Weight of evidence
Test Substance	DPX-HGW86-230; batch, HGW86-0603-1; purity, 94.5%
Endpoint	LOAEL: 200 ppm (males/females: 6 mg/kg b.w./day) (effects indicative of liver toxicity)
	NOAEL: 40 ppm (males/females: 1 mg/kg b.w./day) *NB: NOAEL/LOAEL revised following secondary CIRCA review – see additional comment below*
Reference	Luckett, E.M. (2010); DPX-HGW86 technical: Chronic toxicity 1-year feeding study in dogs. MPI Research, Inc., Mattawan, Michigan, USA. Laboratory Report No.**:** 125-056; DuPont-19180. August 25, 2010. MRID 48119960. Unpublished. Mawn, M.P. (2010); DPX-HGW86 technical: Chronic toxicity 1-year feeding study in dogs. DuPont Haskell Laboratories; MPI Research, Inc., Newark, Delaware, USA; Mattawan, Michigan, USA. Laboratory Report No.: 125-056. DuPont-19180, Supplement No. 1. September 7, 2010. MRID 48208427. Unpublished (analysis of plasma samples for metabolites). [Also CIRCA]
Klimisch Score	1
Amendments/Deviations	None
GLP	Yes
Test Guideline/s	US EPA OPPTS 870.4100; OECD 452
Species	Dog
Strain	Beagle
No/Sex/Group	4 given all doses, plus 3 in a group dosed at 5,000 ppm for 12 weeks, then recovery
Dose Levels	0, 40, 200, 1000 or 5,000 ppm [mean intakes, males: 0, 1, 6, 27 & 144 mg/kg b.w./day; females: 0, 1, 6, 27 & 133 mg/kg b.w./day]
Study Summary	One 5000 ppm male was euthanized *in extremis* on Day 80. The need for euthanasia was considered to be due to complications associated with arteritis. This death may be test article related as arteritis was observed in other dogs on this study in the 1000 and 5000 ppm groups (and in one control dog), and at

10000 ppm in a previous 90-day study with this test article (MRID 48119948). A 5000 ppm female was also euthanized on day 176, due to clinical signs attributed to septicaemia from unknown cause, which was not attributed directly to test article exposure. Over the entire dosing period, main study animals at 5000 ppm gained less body weight than control (35% less in males and 92% less in females)

Treatment-related increases in alkaline phosphatase (ALP) and alanine aminotransferase (ALT), and decreases in total protein and albumin were observed in male and female animals at dietary concentrations of 1000 and 5000 ppm. Gamma glutamyltransferase (GGT) was also increased in the 5000 ppm male and female groups. At the 1000 and 5000 ppm concentrations, the clinical chemistry changes were associated with evidence of degenerative and inflammatory changes in the liver and, in a few animals, with minimal cholestasis. Test article-related macroscopic observations were observed in one female each at 1000 ppm and 5000 ppm and consisted of discoloration (tan) and/or irregular surface of the liver. Males and females at 1000 ppm and 5000 ppm had increased group mean liver (with gall bladder) weights (absolute, relative to body weight and to brain weight), that were associated with degenerative and inflammatory microscopic changes in the liver Three males and one female at 5000 ppm had minimal to mild hyperplasia of the mucosa of the gall bladder. These clinical and histopathology changes were considered to be test article related and adverse. Liver weights were also increased in the 40 and 200 ppm males and in 200 ppm females, but were considered by the study authors to be adaptive effects, as they were not associated with any clinical or macroscopic pathology evidence of liver toxicity. In the recovery group, these effects were not seen in males or females; however, the finding in the recovery group should not be interpreted as to demonstrate that the effects seen in the 1-year treated dogs were reversible because the dogs in the recovery group were treated with cyantraniliprole for only 12 weeks

Test article-related increases in the incidence of arteritis, particularly in coronary arteries, were observed in males at 1000 ppm (3/4) and 5000 ppm (2/4). The increase in the incidence of arteritis was also seen in the 90-day dog study with this test article (MRID 48119948). Increased thyroid/parathyroid weights were observed in 5000 ppm males and were considered possibly test article related, but not adverse, as there were no associated microscopic pathology effects.

	The results of the supplemental study (Mawn, M.P., 2010) showed that the only detectable analyte in plasma was parent cyantraniliprole and there was no apparent sex difference in plasma concentration for any analyte in any treatment groups. At the week 39, the plasma levels of cyantraniliprole were 62 µg/mL and 57 µg/mL in the 5000 ppm males and females, and for the recovery samples was 19.7 ng/mL and 10.8 ng/mL, respectively. None of the metabolites for which analyses were conducted had quantifiable levels
Additional Comments	Test substance DPX-HGW86-230 was synthesised by an early pre-commercial process that has subsequently been abandoned Following secondary review, the CIRCA evaluation revised the NOAEL from 200 ppm (6 mg/kg b.w/day) to 40 ppm (1 mg/kg b.w./day), and the LOAEL from 1000 ppm (27 mg/kg bw/day) to 200 ppm. This was based on the observation of effects indicative of liver toxicity – decreases in albumin levels, significant increases in absolute and relative liver weight and alkaline phosphatase. At the next dose degenerative and inflammatory changes in the liver were observed
Conclusion	**Under the conditions of this study, cyantraniliprole (batch DPX-HGW86-230) induced/exacerbated arteritis and caused adverse effects in the liver of dogs (LOAEL for liver effects: 6 mg/kg b.w./day). Cyantraniliprole should be classified 6.9B for repeated oral dose Target Organ Systemic Toxicity (Table 17.2; User Guide for Thresholds and Classifications; EPA, 2012), based on the evidence submitted for this study, as the LOAEL adjusted for the extra length of exposure (365/90 days x 6 = 24) is inside the Threshold**

Type of Study	**Combined chronic toxicity / oncogenicity study – 2-year feeding in rats**	
Flag	Weight of evidence	
Test Substance	Cyantraniliprole tech.; batch, DPX-HGW86-41; purity, 97.0%	
Endpoints	Non-Neoplastic Effects (See above for neoplastic effects)	LOAEL: 2000 ppm (males: 84.8 mg/kg b.w./day; females: 1160.8 mg/kg b.w./day) (based on changes in liver histopathology)
		NOAEL: 200 ppm (males: 8.3 mg/kg b.w./day; females: 10.5 mg/kg b.w./day)
Reference	Craig, L. (2011); Cyantraniliprole technical (DPX-HGW86 commercial batch - 412): Combined chronic toxicity/oncogenicity study 2-year feeding study in rats.	

	MPI Research, Inc., Mattawan, Michigan, USA. Unpublished laboratory report No. 125-101. DuPont-26842. April/28/ 2011. MRID 48122577. [Also CIRCA]
Klimisch Score	1
Amendments/Deviations	None significant
GLP	Yes
Test Guideline/s	US EPA OPPTS 870.4300 (1998); OECD Section 4 (Part 453) (1981 and 2009); Commission Directive 88/302/EC Part B.33 (1988)
Species	Rat
Strain	Crl:CD(SD)
No/Sex/Group	70 (10 per group for 12-month chronic toxicity study)
Dose Levels	0, 20, 200, 2,000 or 20,000 ppm [mean intakes, males: 0, 0.8, 8.3, 84.8, & 906.6 mg/kg b.w./day; females: 0. 1.1, 10.5, 106.6, 1160.8 mg/kg b.w./day]
Exposure Type	Diet
Study Summary	No test article-related effects were noted in clinical pathology parameters at <2000 ppm. At the 12-month interval a few male animals at 20,000 ppm exhibited moderate increases in GGT (gamma glutamyltransferase), AST (aspartate aminotransferase), ALT (alanine aminotransferase), and sorbitol dehydrogenase relative to expected ranges. This collection of changes were considered test article-related and correlates to the histopathologic changes in the liver Following the one year interim, test article-related increased mean liver weights occurred in both male and female rats at 2000 and 20,000 ppm. At the terminal necropsy liver weights were only statistically significantly increased in the 20,000 ppm males. The increased liver weights correlated to hepatocellular hypertrophy noted in both sexes following the interim and terminal necropsies. Hepatocellular hypertrophy was also noted in females at 2000 ppm. This change was likely the result of enzyme induction and was not considered adverse Following two years of exposure to the test article, there was an increase in the incidence of foci of cellular alteration (clear, eosinophilic, and basophilic) and focal vacuolation (morphologically compatible with focal fatty change) at 20,000 ppm in male livers. At 2000 ppm, clear cell foci of cellular alteration and focal vacuolation were also increased, and there was a non-statistically significant increase in eosinophilic foci. At termination, there was an increase in incidence

	and a very minimal increase in severity of chronic progressive nephropathy in the kidneys in females at 20,000 ppm
Additional Comments	No additional comments
Conclusion	**Under the conditions of this study, cyantraniliprole (batch DPX-HGW86-41) induced adverse effects in the liver of rats (LOAEL: 84.8 mg/kg b.w./day). Cyantraniliprole should be not classified for repeated oral dose Target Organ Systemic Toxicity (Table 17.2; User Guide for Thresholds and Classifications; EPA, 2012), based on the evidence submitted for this study, as the LOAEL adjusted for the extra length of exposure (730/90 days x 84.8 = 688) is outside the Threshold**

Type of Study	**Acute Neurotoxicity Study – gavage, rat**
Flag	Weight of evidence
Test Substance	DPX-HGW86-149; batch, H-22703-312; purity, 97.2%
Endpoint	LOAEL: >2,000 mg/kg b.w.
	NOAEL: 2,000 mg/kg b.w.
Reference	Malley, L.A. (2006); DPX-HGW86 technical: Acute oral neurotoxicity study in rats. DuPont Haskell Laboratories, Newark, Delaware, USA. Laboratory Report No.: duPont-16996. April 19, 2006. MRID 48119950. Unpublished. [Also CIRCA]
Klimisch Score	1
Amendments/Deviations	None
GLP	Yes
Test Guideline/s	US EPA OPPTS 870.6200 (1998)
Species	Rat
Strain	Crl:CD(SD)IGS BR
No/Sex/Group	12
Dose Levels	0, 250, 1000 or 2000 mg/kg b.w. by gavage
Study Summary	Unscheduled mortality did not occur during the study There were no test substance-related effects on clinical signs of toxicity, body weight, weight gain, or food consumption

	Under the conditions of this study, no test substance-related changes were found in any treatment groups for the following evaluations: body weight, body weight gain, food consumption, food efficiency, mortality, clinical observations, forelimb or hindlimb grip strength, hind limb foot splay, body temperature, rearing, duration or number of movements, or any of the other behavioural parameters in the FOB. No test substance-related gross or microscopic morphological changes were observed in either males or females administered any dosage of the test substance. Minimal axonal degeneration was diagnosed in a total of seven nerves (one control male, one 2000 mg/kg b.w. male, and one 2000 mg/kg b.w. female). In all cases, only one or two nerve fibres were involved. These focal lesions, which are typical of background lesions in rats of this age and strain, were not considered to be test substance related
Additional Comments	No additional comments
Conclusion	**Cyantraniliprole (batch DPX-HGW86-149) did not show any specific acute neurotoxic effects in rats, based on the evidence submitted**

Type of Study	**Subchronic Neurotoxicity Study – 90-day feeding, rats**
Flag	Weight of evidence
Test Substance	DPX-HGW86-230; batch, HGW86-0603-1; purity, 94.5%
Endpoint	LOAEL: >20,000 ppm
	NOAEL: 20,000 ppm (males: 1195 mg/kg b.w./day; females: 1404 mg/kg b.w./day)
Reference	Mukerji, P. (2009); DPX-HGW86 technical: Subchronic oral neurotoxicity study in rats. DuPont Haskell Laboratories, Newark, Delaware, USA. Laboratory Report No.: DuPont-19186. Feb. 5, 2009. MRID 48119966. Unpublished. [Also CIRCA]
Klimisch Score	1
Amendments/Deviations	None
GLP	Yes
Test Guideline/s	U.S. EPA OPPTS 870.6200 (1998); OECD 424 (1997); EC Guideline Directive 2004/73/EC Method B.43 (2004)
Species	Rat

Strain	Crl:CD(SD)
No/Sex/Group	12
Dose Levels	0, 200, 2000 or 20,000 ppm [mean intakes, males: 0, 11.4, 115.7 & 1194.8 mg/kg b.w./day; females: 0, 14, 137 & 1403.8 mg/kg b.w./day]
Study Summary	Under the conditions of the study, there were no test substance related effects on body weights, body weight gains, food consumption, food efficiency, clinical signs of toxicity, survival, neurobehavioral parameters, or gross and microscopic morphology of the nervous system, in either male or female rats administered up to 20,000 ppm of test substance in the diet
Additional Comments	Test substance DPX-HGW86-230 was synthesised by an early pre-commercial process that has subsequently been abandoned
Conclusion	**Cyantraniliprole (batch DPX-HGW86-230) did not show any specific sub-acute neurotoxic effects in rats, based on the evidence submitted**

Type of Study	**Immunotoxicity – 28-day, feeding rats**
Flag	Weight of evidence
Test Substance	DPX-HGW86-230; batch, HGW86-0603-1; purity, 94.5%
Endpoint	LOAEL: >20,000 ppm
	NOAEL: 20,000 ppm (males: 1699 mg/kg b.w./day; females: 1703 mg/kg b.w./day)
Reference	Hoban, D. (2009). Cyantraniliprole (DPX-HGW86) Technical: 28-Day Immunotoxicity Feeding Study in Rats. DuPont Haskell Laboratories, Newark, Delaware 19714, USA. Laboratory Report No.: DuPont-21467. 10 April 2009. MRID 48119971. Unpublished. [Also CIRCA]
Klimisch Score	1
Amendments/Deviations	None
GLP	Yes
Test Guideline/s	US EPA OPPTS 870.7800 (1998)
Species	Rat
Strain	Crl:CD(SD)
No/Sex/Group	10

Dose Levels	0, 20, 200, 2000 or 20,000 ppm [mean intakes, males: 0, 1.7, 17, 166 & 1699 mg/kg b.w./day; females: 0, 1.8, 18, 172 & 1703 mg/kg b.w./day]
Study Summary	In the treated animals there were no unscheduled mortalities in any treatment group; there were no treatment-related effects on body weight, body weight gain, food consumption, food efficiency, or organ weights (i.e. spleen, thymus, and brain); and there were no treatment related findings for clinical signs of toxicity or macroscopic pathology The sheep red blood cells (SRBC)-specific IgM ELISA results did not indicate any treatment-related immunosuppressive effects. There were no statistical differences in quantity of SRBC-specific IgM in any treatment group when compared with the vehicle controls. Evaluation of individual animal data did not show any trend or distribution that would demonstrate significant suppression of SRBC-specific antibody response. The positive control (25 mg/kg b.w./day cyclophosphamide monohydrate intraperitoneally for 6 days) performed as expected with an immune response 20% and 22% of the control (100%), for males and females respectively
Additional Comments	Test substance DPX-HGW86-230 was synthesised by an early pre-commercial process that has subsequently been abandoned
Conclusion	**Cyantraniliprole (batch DPX-HGW86-230) did not show any specific sub-acute immunotoxic effects in rats, based on the evidence submitted**

Type of Study	**Immunotoxicity – 28-day, feeding mice**
Flag	Weight of evidence
Test Substance	DPX-HGW86-230; batch, HGW86-0603-1; purity, 94.5%
Endpoint	LOAEL: >20,000 ppm
	NOAEL: 20,000 ppm (males: 1065 mg/kg b.w./day; females: 1386 mg/kg b.w./day)
Reference	Hoban, D. (2011). Cyantraniliprole (DPX-HGW86) Technical: 28-Day Immunotoxicity Feeding Study in Mice. DuPont Haskell Laboratories, Newark, Delaware 19714, USA. Laboratory Report No.: DuPont-21468, Revision No. 1. 11 April 2011. MRID 48119972. Unpublished. [Also CIRCA]
Klimisch Score	1
Amendments/Deviations	None
GLP	Yes

Test Guideline/s	US EPA OPPTS 870.7800 (1998)
Species	Mice
Strain	Crl:CD1(ICR)
No/Sex/Group	10
Dose Levels	0, 20, 150, 1000 or 7,000 ppm [mean intakes, males: 0, 3.0, 23, 154 & 1065 mg/kg b.w./day; females: 0, 4.1, 32, 154 & 1386 mg/kg b.w./day]
Study Summary	In the treated animals there were no unscheduled mortalities in any treatment group; there were no treatment-related effects on body weight, body weight gain, food consumption, or food efficiency; there were no dose-related effects on organ weights (i.e. spleen, thymus, and brain); and there were no treatment related findings for clinical signs of toxicity or macroscopic pathology The SRBC-specific IgM ELISA results did not indicate any treatment-related immunosuppressive effects. There were no statistical differences in quantity of SRBC-specific IgM in any treatment group when compared with the vehicle controls. Evaluation of individual animal data did not show any trend or distribution that would demonstrate significant suppression of SRBC-specific antibody response. The positive control (25 mg/kg b.w./day cyclophosphamide monohydrate intraperitoneally for 5 days) performed as expected with an immune response 52% and 58% of the control (100%), for males and females, respectively
Additional Comments	Test substance DPX-HGW86-230 was synthesised by an early pre-commercial process that has subsequently been abandoned
Conclusion	**Cyantraniliprole (batch DPX-HGW86-230) did not show any specific sub-acute immunotoxic effects in mice, based on the evidence submitted**

Type of Study	**Mechanistic Study – adrenal and thyroid, 90-day feeding rat**
Flag	Weight of evidence
Test Substance	DPX-HGW86-230; batch, HGW86-0603-1; purity, 94.5%
Endpoint	LOAEL: > 20,000 ppm
	NOAEL: 20,000 ppm (males: 1230 mg/kg b.w./day; females: 1903 mg/kg b.w./day)
Reference	MacKenzie, S.A. (2010a); Cyantraniliprole (DPX-HGW86) technical: Adrenal and thyroid mechanistic: 90-day feeding study in rats. DuPont Haskell Laboratories; Newark, Delaware, USA. Experimental Pathology Laboratories,

	Inc.; Durham, North Carolina, USA; Laboratory for Advanced Electron and Light Optical Methods (LAELOM), Raleigh, North Carolina, USA. Laboratory Report No.: DuPont-24319. May 20, 2010. MRID 48119973. Unpublished. [Also CIRCA]
Klimisch Score	1
Amendments/Deviations	Not applicable
GLP	Yes
Test Guideline/s	None
Species	Rat
Strain	Crl:CD(SD)
No/Sex/Group	15 Females & 10 Males
Dose Levels	0 or 20,000 ppm (females: 1903 mg/kg b.w./day for 29 days; males: 1230 mg/kg b.w./day for 93 days)
Study Summary	Under the conditions of this study, cyantraniliprole at 20,000 ppm produced no effects on survival rates, food consumption, and clinical observations in either males or females. However, the 20,000 ppm female rats showed lower body weight, body weight gain and food efficiency compared to controls. In 20,000 ppm females thyroid endpoints (hormone evaluations, anatomic pathology, organ weights, and hepatic biochemistry) were evaluated. Increased liver and thyroid weights and minimal thyroid follicular cell hypertrophy were seen. These effects were associated with increased hepatic UDP-glucuronyltransferase (UDPGT) activity and alterations in thyroid hormone homeostasis including reduced serum T_4 concentration and increased TSH levels. These findings appeared to support the idea that the thyroid effects seen in the 90-day study with cyantraniliprole might be a consequence of increased hepatic enzyme activity. The increased hepatic enzyme activity facilitated clearance of T_4, leading to lower T_4 levels, reduced negative feedback on hypothalamus and pituitary, and subsequent increased TSH stimulation of the thyroid gland. A reduction in hepatic microsomal 5′-deiodinase activity was also observed; however, the biological significance of this reduced activity was unclear, in the absence of any difference in T_3 or reverse T_3 (rT_3) levels. In 20,000 ppm male rats adrenal endpoints (urine corticosterone, adrenal response to ACTH, organ weights, and anatomic pathology) were evaluated. An increase in the incidence of microvesiculation (4/10) of the adrenal cortex

	with no evidence of cytotoxicity or degeneration was found. A minimal to mild increase in adrenal cytoplasm lipid vacuoles was observed by electron microscopy, but no effects on cellular organelles or evidence of cytotoxicity or degeneration were observed. In addition, microvesiculation was not associated with changes in adrenal cortical function, as basal urinary corticosterone and ACTH-induced serum corticosterone levels were comparable among all treatment groups
Additional Comments	Test substance DPX-HGW86-230 was synthesised by an early pre-commercial process that has subsequently been abandoned
Conclusion	**Cyantraniliprole at 20,000 ppm in the diet induced an increase in hepatic UDP-glucuronyl transferase activity in female rats that through feedback on the hypothalamus and pituitary produced the observed changes in the thyroid. 20,000 ppm dietary cyantraniliprole to male rats did not affect adrenal cortical cell structure or function at an exposure level that produced increased adrenal cortex microvesiculation**

Type of Study	**Mechanistic Study – adrenal, 90-day feeding mouse**
Flag	Weight of evidence
Test Substance	DPX-HGW86-141; batch, E2000077-0324A; purity, 91.5%
Endpoint	LOAEL: >7,000 ppm
	NOAEL: 7,000 ppm (1120 mg/kg b.w./day)
Reference	MacKenzie, S.A. (2010b); Cyantraniliprole (DPX-HGW86) technical: Adrenal mechanistic study 90-day feeding study in mice. DuPont Haskell Laboratories, Newark, Delaware, USA; Experimental Pathology Laboratories, Inc.; Laboratory for Advanced Electron and Light Optical Methods (LAELOM), Durham, North Carolina, Raleigh, North Carolina, USA. Laboratory Report No.: DuPont-29405. MRID 48119985. Unpublished. [Also CIRCA]
Klimisch Score	1
Amendments/Deviations	Not applicable
GLP	Yes
Test Guideline/s	None
Species	Mouse
Strain	Crl:CD1

No/Sex/Group	10 Males
Dose Levels	0 or 7,000 ppm (1120 mg/kg b.w./day for 93 days)
Study Summary	No deaths occurred, and no clinical observations were attributed to test substance exposure. Exposure to 7,000 ppm produced no adverse effects on body weight or nutritional parameters in treated mice. Lower overall mean body weight gain (not statistically significant) and food efficiency (statistically significant) were observed in treated mice but were not considered adverse as there were no significant differences in mean final body weight. No effects on food consumption were observed. Urine corticosterone (absolute corticosterone and corticosterone/creatinine ratio) was comparable between treated and control mice. In treated mice, urine creatinine and corticosterone were higher than in control when expressed per mL, but this was due to lower urine volume in treated mice. No difference in adrenal gland weight (absolute or relative to body weight) was observed between treated and control groups. No gross or microscopic pathology effects were attributed to test substance exposure. Minimal microvesiculation, considered a background finding, was observed in the adrenal cortex of all control and treated mice, but the incidence and severity were not increased in the treated group, as was observed in the 90-day feeding study in mice [DuPont-16992; MRID 48119943]. Electron microscopic evaluation of selected adrenal glands confirmed the lack of ultrastructural effects in any cellular organelles and no evidence of cell injury or degeneration in the adrenal cortex
Additional Comments	The finding of the microvesiculation of the adrenal cortex in male mice at ≥ 50 ppm in the 90-day study (MRID 48119943) was not duplicated in this study, where male mice were fed a dietary concentration of 7000 ppm (1120 mg/kg b.w./day) of cyantraniliprole for 93 days
Conclusion	**Under the conditions of this study, no adverse effects on adrenal cortical structure or function were observed following dietary exposure to 7000 ppm, a concentration that produced a small increase in the incidence of increased adrenal cortical microvesiculation in a previous 90-day study**

Type of Study	**Mechanistic Study – thyroid, *in vitro***
Flag	Weight of evidence
Test Substance	DPX-HGW86-230; batch, HGW86-0603-1; purity, 94.5%

Endpoint	LOAEL: NA
	NOAEL: NA
Reference	Snajdr, S.I. (2010); Cyantraniliprole (DPX-HGW86) technical: *In vitro* thyroid peroxidase inhibition. Dupont Haskell Laboratories, Newark, Delaware, USA. Laboratory Report No.: DuPont-27123. September 9, 2010. MRID 48119979. Unpublished. [Also CIRCA]
Klimisch Score	1
Amendments/Deviations	Not applicable
GLP	Yes
Test Guideline/s	None
Species	Yucatan pig (microswine)
Strain	NA
No/Sex/Group	NA
Dose Levels	Concentrations ranging from 2 to 400 μM
Study Summary	In thyroid hormone synthesis, thyroid peroxidase catalyzes the first two steps, oxidation of iodide to iodine and the iodination of tyrosine residues on thyroglobulin. Inhibition of thyroid peroxidase disrupts the homeostasis of the hypothalamic-pituitary-thyroid axis. This study (MRID 48119979) was designed to evaluate the ability of cyantraniliprole to inhibit thyroid peroxidase activity *in vitro* using thyroid preparations from the Yucatan pig (microswine). Cyantraniliprole concentrations ranging from 2 to 400 μM were tested; the maximum concentration was the level where limit of solubility was present in the assay system. Propylthiouracil (PTU), a known thyroid peroxidase inhibitor, was the positive control. The result showed that for PTU, the concentration that caused a 50% reduction in enzyme activity (IC_{50}) was 7.3 μM. In contrast cyantraniliprole did not cause inhibition of thyroid peroxidase at any concentration tested; therefore, an IC_{50} value for cyantraniliprole was unable to be determined
Additional Comments	Test substance DPX-HGW86-230 was synthesised by an early pre-commercial process that has subsequently been abandoned
Conclusion	**Under the conditions of this *in vitro* study, cyantraniliprole did not inhibit thyroid peroxidase**

Type of Study	**ADME – single oral dose, rat**
Flag	Supporting study
Test Substance	[CN-^{14}C]-cyantraniliprole; lot, HGW86 3503-242; radiochemical purity, 99% [PC-^{14}C]-cyantraniliprole; lot, HGW86 3503-247; radiochemical purity, 99% DPX-HGW86-141; batch, E2000077-0324A; purity, 91.5%
Endpoint	LOAEL: NA
	NOAEL: NA
Reference	Gannon, S.A. (2010); ^{14}C-DPX-HGW86: Absorption, distribution, metabolism and excretion in male and female rats. DuPont Haskell Laboratories, Newark, Delaware, USA., DuPont-16995, Revision No. 1. MRID 48119949. Unpublished. [Also CIRCA].
Klimisch Score	1
Amendments/Deviations	None
GLP	Yes
Test Guideline/s	U.S. EPA OPTTS 870.7485 (1998); OECD Section 4 Prt (417; 1984); Annex to Directive 87/302/EEC, Part B, Toxicokinetic (1987)
Species	Rat
Strain	Crl:CD(SD)
No/Sex/Group	4
Dose Levels	10 or 150 mg/kg b.w. by gavage
Study Summary	The data indicated that cyantraniliprole was absorbed readily either at low (10 mg/kg b.w.) or high (150 mg/kg b.w.) dose with oral dosing. The majority of the absorption occurred during the first 48 hours, and the peak plasma concentration was reached at approximately 2 hours after dosing irrespective of the position of label, sex of the test animal, and dose level. Both species of radiolabeled cyantraniliprole exhibited very similar kinetics (male low dose half-lives: CN $T_{1/2}$ = 42 hrs; PC $T_{1/2}$ = 54 hrs; female low dose half-lives: CN $T_{1/2}$ = 129 hrs; PC $T_{1/2}$ = 117 hrs; male high dose half-lives: CN $T_{1/2}$ = 62 hrs; PC $T_{1/2}$ = 55 hrs; females high dose half-lives: CN $T_{1/2}$ = 65 hrs; PC $T_{1/2}$ = 80 hrs). The values of C_{max} and area-under-the-curve (AUC) demonstrated a greater internal dose in female rats than in male rats. With dose-normalized AUC, the data suggested a decrease in absorption at high dose in comparison to the low dose.

The distribution of ^{14}C residues was evaluated as the percentage of the administered dose, concentration of ^{14}C equivalents per gram of tissue, and tissue:plasma concentration ratios at T_{max}, $T_{max}/2$, and terminal sacrifice after single oral dose administration. There was no appreciable difference between dosing with the [CN-^{14}C]-cyantraniliprole or [PC-^{14}C]-cyantraniliprole label in terms of tissue distribution. The majority of the dose was initially associated with the GI tract contents and subsequently showed uptake and distribution to all tissues. The percent recovery and tissue concentration data showed that female rats retained a greater proportion of ^{14}C residues than male rats. The declines of the plasma and tissue ^{14}C residue concentrations at high and low doses were generally similar. These observations were consistent with the shorter elimination half-life in male rats compared with female rats. The tissue:plasma concentration ratios were less than or equal to 1 by 168 hours after dose administration. Many of the tissue:plasma concentration ratios were below 1 at the $T_{max}/2$ time point as well.

The bile cannulation study showed that there was no appreciable difference between the two forms of radiolabeled cyantraniliprole. The mean total recovery of absorbed and unabsorbed (faeces, cage wash, and GI tract contents) radioactivity accounted for 89.0 to 101.6% of the dose. Absorption was considerably higher at the 10 mg/kg b.w. dose level in which 75.8 to 80.4% and 62.6 to 74.9% of the dose was measured for male and female rats, respectively, compared with 38.8 to 40.0% and 31.4 to 32.2% of the dose for male and female rats administered cyantraniliprole at 150 mg/kg b.w., respectively.

Metabolism results suggested that cyantraniliprole was readily hydroxylated to form IN-N7B69 and IN-MYX98. IN-N7B69 was further metabolized to a glucuronide. Cyantraniliprole also underwent ring closure to generate IN-J9Z38 which was hydroxylated to form IN-NBC94, its carboxylic acid, and its glucuronide conjugate. IN-MYX98 was also metabolized to the closed-ring metabolite IN-MLA84, which, like IN-NBC94, was further oxidized to a hydroxylated metabolite, a carboxylic acid, and the glucuronide of the hydroxyl metabolite. Further, the hydroxylated metabolite IN-MYX98 could be N-dealkylated to form IN-HGW87 as well as being hydroxylated a second time to form bis-hydroxy-HGW86. Cyantraniliprole could also be hydroxylated on the pyridine ring, followed by a ring closure analogous to the conversion of cyantraniliprole to IN-J9Z38. Cyantraniliprole could also be N-dealkylated and cleaved at the carbonyl bridge to form IN-DBC80. The metabolites which were

	found to be greater than 5% of the administered dose were bis-hydroxy-cyantraniliprole, IN-N7B69, IN-MYX98, INDBC80, and the parent compound. There was very little difference in elimination between rats administered [CN-^{14}C]-cyantraniliprole or [PC-^{14}C]-cyantraniliprole. Rats given a single 10 mg/kg b.w. dose of either species of cyantraniliprole excreted a greater percentage of the dose in urine (22.0 to 34.6%) than rats dosed with 150 mg/kg b.w. (11.8 to 14.8%). For both dose levels and labels, the majority of the dose was excreted by 24 to 48 hours after administration. The percent recovery in rats at the 10 mg/kg b.w. dose level was 22.0 to 34.6% for urine, 46.8 to 61.6% for faeces, and 1.1 to 5.3% for tissues. Lower absorption from the GI tract occurred in rats given the 150 mg/kg b.w. dose as indicated by the lower percentage of the dose in tissues (0.25 to 2.5%) and urine (11.8 to 14.8%), and the greater percentage of the dose excreted in the faeces (77.6 to 80.1%). For all groups in which material balance was measured, the mean percentage for total recovery by 7 days after dosing ranged from 88.3 to 96.5%. The data also indicate that there was no appreciable tendency for bioaccumulation to occur for cyantraniliprole
Additional Comments	No additional comments
Conclusion	The data indicated that with oral administration of cyantraniliprole at low and high doses, it was absorbed readily. The majority of the absorption occurred during the first 48 hours and the peak plasma concentration was reached at approximately 2 hours after dosing irrespective of the position of label, sex of the test animal, and dose level. However, with the low dose the $T_{1/2}$ was lower in male relative to females. The values of AUC were also substantially smaller in male than in females. With dose-normalized AUC, the data suggested a decrease in absorption at high dose in comparison to the low dose. The majority of the dose was initially associated with the GI tract contents and subsequently showed uptake and distribution to all tissues. The percent recovery and tissue concentration data showed that female rats retained a greater proportion of ^{14}C residues than male rats. After 168 hours following dosing, skin, liver, and muscle generally have slightly higher residue level than other tissues examined, but the level expressed as percentage of the administered dose was less than 1%. Cyantraniliprole was metabolised via several pathways. The metabolites which were found to be greater than 5% of the administered dose were bis-hyroxy-cyantraniliprole, IN-N7B69, IN-MYX98, INDBC80, and the parent compound. There was essentially no difference in elimination between rats administered [CN-^{14}C]-cyantraniliprole or [PC-^{14}C]-cyantraniliprole. Rats given a single 10

	mg/kg b.w. dose of either species of cyantraniliprole excreted a greater percentage of the dose in urine than rats dosed with 150 mg/kg b.w. For both dose levels and labels, the majority of the dose was excreted by 24 to 48 hours after administration. The percent recovery in rats at the 10 mg/kg b.w. dose level was 22.0 to 34.6% for urine, 46.8 to 61.6% for faeces, and 1.1 to 5.3% for tissues. When rats were given 150 mg/kg b.w., a greater percentage of the dose was excreted in the faeces (77.6 to 80.1%). For all groups in which material balance was measured, the mean percentage for total recovery by 7 days after dosing ranged from 88.3 to 96.5%. The data also indicate that there was no appreciable tendency for bioaccumulation to occur for cyantraniliprole

Type of Study	**ADME – multiple (14) oral doses, rat**
Flag	Supporting study
Test Substance	[CN-^{14}C]-cyantraniliprole; lot, HGW86 3503-242; radiochemical purity, 99% [PC-^{14}C]-cyantraniliprole; lot, HGW86 3562-048; radiochemical purity, 98.1% DPX-HGW86-141; batch, E2000077-0324A; purity, 93.4%
Endpoint	LOAEL: NA
	NOAEL: NA
Reference	Gannon, S.A. (2010); ^{14}C-DPX-HGW86: Disposition in male and female rats during and after multiple dose administration. DuPont Haskell Laboratories, Newark, Delaware, USA. Laboratory Report No. DuPont-17399, Revision No. 1. Original report completion: July 16, 2009. Report Revision 1 completed: Dec. 02, 2010. MRID 48119951. Unpublished. [Also CIRCA]
Klimisch Score	1
Amendments/Deviations	None
GLP	Yes
Test Guideline/s	U.S. EPA OPTTS 870.7485 (1998); OECD Section 4 Prt (417; 1984); Annex to Directive 87/302/EEC, Part B, Toxicokinetic (1987)
Species	Rat
Strain	Crl:CD(SD)
No/Sex/Group	3 (each time-point)
Dose Levels	10 mg/kg b.w. by gavage

Study Summary	Concentration (μg equiv/g), tissue:plasma ratio, and percent of dose were calculated for tissues collected from male and female rats at various times during and after exposure. The data on the tissue concentrations and the tissue percent recovery showed that tissue concentration fell rapidly following the end of dosing. The tissue concentration half-lives ranged from 2.6 days in fat to approximately 6 days in whole blood. The tissue:plasma ratios were all less than 1 following the end of the dosing period. The short tissue half-lives and the tissue:plasma ratio indicated that there was very little tissue accumulation. The cumulative excretion of total radioactivity in urine and faeces was evaluated from Day 1 through Day 20 as both the percent of accumulating dose and the percent of total dose. The accumulating dose in urine, which represents the amount excreted in the urine in a 24 hr period, ranged from 24 to 29% in males and 13 to 20% in females. The total percent of dose eliminated in the urine was 29% in male rats and 20% in female rats. The accumulating dose in faeces ranged from 43 to 61% in males and 42 to 62% in females. The total percent of dose eliminated in the faeces was 61% in males and 62% in females. Metabolites in urine and faeces during and following multiple dosing were the same as those observed in the single oral dose study (MRID 48119949). In most cases there was very little difference observed between metabolite distribution on Day 1, 7, or 14 in urine metabolites. In urine from male rats IN-N7B69 was present at approximately 5% of the dose on Day 1 and 7 but was not detected on Day 14. It was not detected on any day in female rat urine. IN-MYX98 was present only at 0.5% of the administered dose in male urine on Day 1, but was present at significantly higher levels by Day 7 (5% of dose) and Day 14 (3% of dose). In contrast, this same metabolite was present at 7% on Day 1, 11% on Day 7, but only 1% on Day 14 in female rat urine. Cyantraniliprole was approximately 5% of the dose in female rat urine on Days 1 and 7, but not detected on Day 14. IN-MLA84 in female urine was less than 1% of the dose for Days 1 and 7, but was 14% of the dose on Day 14. Compared to the urinary metabolites, the most notable differences in faecal metabolite profile both occurred in the female rat samples. There was an increase in both IN-MLA84 (Day 1, 1%; Day 14, 5% of dose) and in IN-MYX98 (Day 1, 10%; Day 14, 16%) as percent of dose. Parent cyantraniliprole was present in male and female faeces from 7% to 19% of the administered dose. Cyantraniliprole is readily hydroxylated to form IN-N7B69 and IN-MYX98. IN-N7B69 is further metabolized to a glucuronide. Cyantraniliprole undergoes ring

	closure to generate IN-J9Z38, which is then in turn hydroxylated to form IN-NBC94, its carboxylic acid, and its glucuronide conjugate. IN-MYX98 is also metabolized to the closed-ring metabolite IN-MLA84, which like IN-NBC94, is further oxidized to a hydroxylated metabolite, a carboxylic acid, and the glucuronide of the hydroxyl metabolite. Further, the hydroxylated metabolite IN-MYX98 can be N-dealkylated to form IN-HGW87 as well as being hydroxylated a second time to form bis-hydroxy-cyantraniliprole. Cyantraniliprole can also be hydroxylated on the pyridine ring, followed by a ring closure analogous to the conversion of cyantraniliprole to IN-J9Z38. Cyantraniliprole can also be N-dealkylated and cleaved at the carbonyl bridge to form IN-DBC80
Additional Comments	No additional comments
Conclusion	The data show that the tissue concentrations and the tissue percent recovery fall rapidly following the end of dosing. Tissue elimination half-lives in females range from 2.6 days in fat to approximately 6 days in whole blood. The lack of accumulation was further confirmed by looking at the entire collection of tissues collected at Day 15 and Day 21 from both male and female rats. The concentration and percent recovery data show decreases with time. The tissue:plasma ratio are all less than 1 following the end of the dosing period, once again indicating there is no accumulation in tissue following the end of the dosing phase. The cumulative excretion of total radioactivity as the accumulating dose in urine ranged from 24 – 29% in males and 13 – 20% in females. The total percent of dose eliminated in the urine was 29% in male rats and 20% in female rats. The accumulating dose in faeces ranged from 43 – 61% in males and 42 – 62% in females. The total percent of dose eliminated in the faeces was 61% in males and 62% in females. The overall percent recovery was 93% in males and 89% in females with the majority of the dose eliminated in faeces. The amount remaining in the tissues at sacrifice was very small (0.8% in males and 2.5% in females). Metabolites in urine and faeces during and following multiple dosing were the same as those observed in the single oral dose study. In most cases there was very little difference observed between metabolite distribution on Day 1, 7, or 14 in urine or faeces metabolites

Type of Study	**Toxicokinetics – multiple (14) oral doses, rat**
Flag	Supporting study

Test Substance	Cyantraniliprole tech.; batch, HGW86-014; purity, ~100%
Endpoint	LOAEL: >1,000 mg/kg b.w./day
	NOAEL: 1,000 mg/kg b.w./day
Reference	Nabb, D.L. (2010); Cyantraniliprole (DPX-HGW86) technical: Repeated-dose oral toxicity 2-week gavage study in rats with metabolism and genetic toxicology. DuPont Haskell Laboratories, Newark, Delaware, USA; Experimental Pathology Laboratories, Inc., Herndon, Virginia, USA. Laboratory Report No.**:** DuPont-13430. Revision No. 1. March 2, 2010. MRID 48119938. Unpublished. [Also CIRCA]
Klimisch Score	1
Amendments/Deviations	Not applicable
GLP	No
Test Guideline/s	None
Species	Rat
Strain	Crl:CD(SD) IGS BR
No/Sex/Group	5 (in main & metabolism studies)
Dose Levels	0, 25, 300 or 1000 mg/kg b.w./day by gavage
Study Summary	The results showed no adverse test substance-related effects on clinical pathology (haematology, clinical chemistry, and urinalysis), gross examination, histopathology, and organ weights. Increases in relative liver and adrenal weight were observed in the 1000 mg/kg b.w./day females. As there was no histomorphologic correlate detected, these organ weight changes were considered test substance related but not adverse. No increases in the frequency of micronucleated PCEs were observed in bone marrow of male or female rats at any dose level. There were no significant effects on TSH, T_3, or T_4 measurements at any dose level. In the toxicokinetic assessment, the area under the plasma concentration *versus* time curve (AUC) was not proportional to the dose of cyantraniliprole at all time-points. The half-life was estimated to be 3.84, 6.41, and 5.44 hours for the 25, 300, and 1000 mg/kg b.w./day dose groups. The time of maximum concentration (T_{max}) was 2.00, 2.33, and 1.67 hours in the 25, 300, and 1000 mg/kg b.w./day groups. The maximum concentration (C_{max}) was 15.53, 7.80, and 6.99 in the 25, 300, and 1000 mg/kg b.w./day groups. Based on the estimated half-life for cyantraniliprole, it was expected that there would be rapid clearance of the parent compound after 2 weeks of dosing. The concentration

	of cyantraniliprole in the perirenal fat was 0.016 and 0.062 μg/mL 24 hours after the final dose on test day 14 in the 25 and 300 mg/kg b.w./day dose groups respectively [under the study design, no fat samples were taken from the high-dose group]. Total cytochrome P450 content in male or female rats was minimally elevated, but not statistically significant, at 1000 mg/kg b.w./day. In male rats, cyantraniliprole was an inducer of cytochrome P450 isozyme CYP1A1 and CYP2B1. In female rats, cyantraniliprole was an inducer of cytochrome P450 isozyme CYP2B1. The study authors concluded that this enzyme induction was test substance-related but not adverse
Additional Comments	No additional comments
Conclusion	The no-observed-adverse-effect level (NOAEL) was 1000 mg/kg b.w./day, the highest dose tested. There were no increases in the frequency of micronucleated PCEs in peripheral blood of male or female rats at any dose level. In the toxicokinetic assessment, the area under the plasma concentration *versus* time curve (AUC) was not proportional to the dose of cyantraniliprole at all time-points. The half-life was estimated to be 3.84, 6.41, and 5.44 hours; the time of maximum concentration (T_{max}) was 2.00, 2.33, and 1.67 hours; the maximum concentration (C_{max}) was 15.53, 7.80, and 6.99 in the 25, 300, and 1000 mg/kg b.w./day groups. Based on the estimated half-life for cyantraniliprole, it was expected that there would be rapid clearance of the parent compound after 2 weeks of dosing. The concentration of cyantraniliprole in the perirenal fat was 0.016 and 0.062 μg/mL 24 hours after the final dose on test day 14 in the 25 and 300 mg/kg b.w./day dose groups respectively. Total cytochrome P450 content in male or female rats was minimally elevated, but not statistically significant, at 1000 mg/kg b.w./day. In male rats, cyantraniliprole induced of cytochrome P450 isozyme CYP1A1 and CYP2B1, and in female rats, isozyme CYP2B1. This enzyme induction was considered by the study authors to be test substance-related but not adverse

General conclusion about target organ systemic toxicity

Acute studies by the oral, dermal and inhalation routes at up to limit doses/concentrations demonstrated that cyantraniliprole did not cause single dose Target Organ Systemic Toxicity (Table 17.1; User Guide for Thresholds and Classifications; EPA, 2012), based on the evidence submitted.

In a sub-acute (4-week) study by the inhalation route, no adverse effects were observed at any of the concentrations tested.

Sub-chronic and chronic studies by the oral route demonstrated that cyantraniliprole can cause target organ systemic toxicity. Adverse effects were predominantly observed in the liver and thyroid. Liver effects were observed in dogs, rats and mice, with dogs the most sensitive species and mice the least affected. The thyroid effects were predominantly found in rats.

In rats, the thyroid appeared the most sensitive target for cyantraniliprole toxicity (increased thyroid weights, thyroid follicular epithelial cell hypertrophy / hyperplasia). These changes appeared to be secondary to the effects on the liver (increased hepatic cytochrome P450 content and UDP-glucuronyltransferase activity leading to decreased plasma thyroid hormone level and alterations in thyroid hormone homeostasis). In the 90-day study in rats (DuPont-16993; MRID 48119945), adaptive to adverse changes in the thyroid were noted, particularly in females. Similar thyroid changes were noted in P1 and F1 females (at ≥ 14 mg/kg b.w./day) and F1 males in the 2-generation reproductive toxicity study in rats (DuPont-19187; MRID 48119967). These changes in the thyroid were not reproduced in the 2-year combined chronic toxicity / oncogenicity feeding study (DuPont-26842; MRID 48122577), or a 90-day mechanistic feeding study (DuPont-24319; MRID 48119973), although the 90-day mechanistic feeding study did reveal adaptive changes in the thyroid at 1903 mg/kg b.w./day in female rats, secondary to adaptive changes in the liver (enzyme induction).

The liver was a target in rats, mice and dogs, possibly the primary target, with changes ranging from adaptive (enzyme induction – sub-toxic doses) to degenerative and inflammatory microscopic changes (with associated clinical chemistry markers) in dogs, the most sensitive species for toxic liver effects. The chronic 1-year feeding study in dogs included a “recovery” satellite group, but this group was only treated for 12 weeks limiting the value of any results from this group. Cyantraniliprole also induced or exacerbated the incidence of arteritis in dogs (Canine Juvenile Polyarteritis).

In the 90-day study in mice (DuPont-16992; MRID 48119943), adaptive changes in the adrenal cortex of males were noted. Similar adrenal changes were noted in P1 males (at ≥ 1.4 mg/kg b.w./day) in the 2-generation reproductive toxicity study in rats (DuPont-19187; MRID 48119967), and in male rats in a 90-day mechanistic feeding study at the limit dose of 1230 mg/kg b.w./day (DuPont-24319; MRID 48119973). However, these changes in the adrenal were not reproduced in a 90-day mechanistic feeding study with male mice (DuPont-29405; MRID 48119985) at the limit dose of 1120 mg/kg b.w./day.

Cyantraniliprole in acute and sub-acute oral studies at up to limit doses did not reveal any specific neurotoxic or immunotoxic effects.

Cyantraniliprole should be classified 6.9B for repeat dose Target Organ Systemic Toxicity (Table 17.2; User Guide for Thresholds and Classifications; EPA, 2012), based on the evidence submitted (liver and thyroid effects).

Table 8 Summary of studies with NOAEL and LOAEL values and key effects.

Study type	NOAEL	LOAEL	Key effect
Sub-chronic toxicity; 90-day diet, rat	Females: 100 ppm (7 mg/kg b.w./day);	Females: 400 ppm (27 mg/kg b.w./day);	Thyroid follicular cell hypertrophy

	Males: 3000 ppm (168 mg/kg b.w./day)	Males: 20,000 ppm (1147 mg/kg b.w./day)	
Sub-chronic toxicity; 90-day diet, mouse	1000 ppm (males: 150 mg/kg b.w./day; females: 204 mg/kg b.w./day)	7000 ppm (males: 1092 mg/kg b.w./day; females: 1344 mg/kg b.w./day)	Focal necrosis of liver and liver weight increases
Sub-chronic toxicity; 90-day diet, dog	100 ppm (males/females: 3 mg/kg b.w./day)	1000 ppm (males: 32 mg/kg b.w./day; females: 34 mg/kg b.w./day)	Clinical chemistry (liver markers)
Chronic toxicity; 1-year diet, dog	**40 ppm (males/females: 1 mg/kg b.w./day)**	**200 ppm (males/females: 6 mg/kg b.w./day)**	**Liver toxicity (decreased albumin levels, increased liver weights and alkaline phosphatase activity)**
Oncogenicity study; 18-month diet, mice	Non-neoplastic: 7,000 ppm Neoplastic: 7,000 ppm (males: 768.8 mg/kg b.w./day; females: 903.8 mg/kg b.w./day)	Non-neoplastic: >7,000 ppm Neoplastic: >7,000 ppm	Non-neoplastic: No adverse effect Neoplastic: No adverse effect
Combined chronic toxicity / oncogenicity study; 2-year diet, rats	Non-neoplastic: 200 ppm (8.3 mg/kg b.w./day) Neoplastic: 20,000 ppm (males: 906.6 mg/kg b.w./day; females: 1160.8 mg/kg b.w./day)	Non-neoplastic: 2000 ppm (84.8 mg/kg b.w./day) Neoplastic: >20,000 ppm	Non-neoplastic: Liver histopathology Neoplastic: No adverse effect
Developmental study – gavage, rats	Maternal: 1000 mg/kg b.w./day Foetal: 1000 mg/kg b.w./day	Maternal >1000 mg/kg b.w./day Foetal: >1000 mg/kg b.w./day	No adverse effect
Developmental study – gavage, rabbits	Maternal: 25 mg/kg b.w./day Foetal: 100 mg/kg b.w./day	Maternal: 100 mg/kg b.w./day Foetal: 250 mg/kg b.w./day	Maternal: diarrhoea; b.w. loss Foetal: ↓ mean b.w.
2-Generation Reproduction study – diet, rats	**Parental: 20 ppm (1.4 mg/kg b.w./day)** Reproductive: 2000 ppm (1344 mg/kg b.w./day) Offspring: 200 ppm (136 mg/kg b.w./day)	**Parental: 200 ppm (14 mg/kg b.w./day)** Reproductive: >2000 ppm Offspring: 2000 ppm	**Parental: Thyroid follicular epithelial cell hypertrophy / hyperplasia** Reproductive: No adverse effect

			Offspring: ↓ thymus and spleen weights
Acute neurotoxicity study – gavage, rat	2000 mg/kg b.w.	>2000 mg/kg b.w.	No adverse effect
Subchronic neurotoxicity study – 90-day feeding, rats	20,000 ppm (males: 1195 mg/kg b.w./day; females: 1404 mg/kg b.w./day)	>20,000 ppm	No adverse effect
Immunotoxicity – 28-day, feeding rats	20,000 ppm (males: 1699 mg/kg b.w./day; females: 1703 mg/kg b.w./day)	>20,000 ppm	No adverse effect
Immunotoxicity – 28-day, feeding mice	7000 ppm (males: 1065 mg/kg b.w./day; females: 1386 mg/kg b.w./day)	>7000 ppm	No adverse effect
Mechanistic study – adrenal and thyroid, 90-day feeding rat	20,000 ppm (males: 1903 mg/kg b.w./day; females: 1230 mg/kg b.w./day)	>20,000 ppm	No adverse effect
Mechanistic Study – adrenal, 90-day feeding mouse	7000 ppm (males: 1120 mg/kg b.w./day)	>7000 ppm	No adverse effect

Mammalian toxicology – Study summaries for the formulations

Unless otherwise noted, all studies were conducted according to GLP and were fully compliant with all requirements of the standard international test methods used.

Acute toxicity and dermal absorption – Benevia

Acute Oral Toxicity [6.1 (oral)]

Type of Study	**Acute oral toxicity – up-down procedure, rat**
Flag	Key study
Test Substance	DPX-HGW86-236; batch, E108803-5; purity, 10.2% w/w
Endpoint	LD_{50}
Value	>5,000 mg/kg b.w.
Reference	Moore, G.E. (2008d). DPX-HGW86 100 g/L OD: Acute Oral Toxicity - Up-and-Down Procedure in Rats. Eurofins PSL, Dayton, New Jersey, USA. Laboratory

	Project ID: EPSL Study Number: 25567. Issue date 12 September 2008. Unpublished. DuPont Report No.: DuPont-26449. US MRID 48120211
Klimisch Score	1
Amendments/Deviations	None
GLP	Yes
Test Guideline/s	US EPA OPPTS 870.1100 (2002); OECD 425 (2006)
Species	Rat
Strain	Sprague Dawley derived
No/Sex/Group	3 Females (fasted)
Dose Levels	5000 mg/kg b.w.
Exposure Type	Gavage
Study Summary	All animals survived, gained body weight, and appeared active and healthy during the study. There were no signs of gross toxicity, adverse pharmacologic effects, or abnormal behaviour. No gross abnormalities were noted for any of the animals when necropsied at the conclusion of the 14-day observation period
Additional Comments	No additional comments
Conclusion	**Cyantraniliprole (DPX-HGW86) 100 g/L OD (Benevia) should not be classified for Acute Oral Toxicity (no marked adverse effects at the limit dose of 5,000 mg/kg b.w.), based on the submitted evidence**

Acute Dermal Toxicity [6.1 (dermal)]

Type of Study	**Acute dermal toxicity – rat**
Flag	Key study
Test Substance	DPX-HGW86-236; batch, E108803-5; purity, 10.2% w/w
Endpoint	LD_{50}
Value	>5,000 mg/kg b.w.
Reference	Moore, G.E. (2008e). DPX-HGW86 100 g/L OD: Acute Dermal Toxicity in Rats. Eurofins PSL, Dayton, New Jersey, USA. Laboratory Project ID: EPSL Study Number: 25568. Issue date 23 September 2008. Unpublished. DuPont Report No.: DuPont-26450. US MRID 48120212
Klimisch Score	1

Amendments/Deviations	None
GLP	Yes
Test Guideline/s	U.S. EPA OPPTS 870.1200 (1998); OECD 402 (1987)
Species	Rat
Strain	Sprague Dawley derived
No/Sex/Group	5
Dose Levels	5,000 mg/kg b.w.
Exposure Type	To shaved, intact skin (semi-occlusive) for 24 hours
Study Summary	All animals survived, gained body weight, and appeared active and healthy during the study. There were no signs of gross toxicity, adverse pharmacologic effects, or abnormal behaviour. No gross abnormalities were noted for any of the animals when necropsied at the conclusion of the 14-day observation period
Additional Comments	No additional comments
Conclusion	**Cyantraniliprole (DPX-HGW86) 100 g/L OD (Benevia) should not be classified for Acute Dermal Toxicity (no marked adverse effects at the limit dose of 5,000 mg/kg b.w.), based on the submitted evidence**

Acute Inhalation Toxicity [6.1 (inhalation)]

Type of Study	**Acute inhalation toxicity – nose only; single 4-hour exposure; aerosol, rats**
Flag	Key study
Test Substance	DPX-HGW86-309; batch, E108803-105; purity, 101.2 g/L
Endpoint	LC_{50}
Value	>3.3 mg/L
Reference	Kegelman, T.A. (2009b). Cyantraniliprole (DPX-HGW86) 100 g/L OD: Inhalation Median Lethal Concentration (LC_{50}) Study in Rats. DuPont Haskell Laboratories, Newark, Delaware, USA. Laboratory Project ID: DuPont-27807 Revision No. 1. Issue date 3 November 2009. Unpublished. DuPont Report No.: DuPont-27807. US MRID 48120215
Klimisch Score	1
Amendments/Deviations	None considered significant
GLP	Yes

Test Guideline/s	US EPA OPPTS 870.1300 (1998); OECD 403 (1981); EEC Method B.2 92/69/EEC (1992)
Species	Rat
Strain	Crl:CD(SD)
No/Sex/Group	5
Dose Levels	3.3 ± 0.23 mg/L aerosol; MMAD (± GSD), 5.9 ± 2.0 µm
Exposure Type	Nose only
Study summary	No mortalities were observed in either male or female rats. Body weight losses (from 1.9 to 15%) were observed in all male and all female rats the day after the exposure. With the exception of one female rat that lost less than one gram on post-exposure day 4, there were no other body weight losses observed in male or female rats throughout the 14-day recovery period. Red nasal and ocular discharge and wet fur were observed in male and female rats for up to 2 days post exposure. One male rat displayed red stained fur on his head from post-exposure day 2 through 4; the stained fur was not observed after post-exposure day 4. Some rats had difficulty removing the test substance from their fur and consequently scratched the fur on their faces, creating hair losses on the face, nose, neck and forelimbs. Two of the 5 male rats had superficial wounds on the neck or head. The hair loss and wounds were observed from post-exposure day 5 until the end of the 14-day recovery period. The clinical signs were more frequent and severe in the male rats
Additional Comments	Difficulties were encountered generating a 5.0 mg/L exposure atmosphere due to the test substance's tendency to stick and adhere to the exposure chamber surfaces. The conditions used to generate the 3.3 mg/L exposure were optimized to generate the highest airborne concentration of the test substance and, therefore, represents the maximum practically-attainable atmospheric aerosol concentration
Conclusion	**Cyantraniliprole (DPX-HGW86) 100 g/L OD (Benevia) should not be classified for Acute Inhalation Toxicity (no marked adverse effects at 3.3 mg/L, the maximum attainable concentration), based on the submitted evidence**

Skin Irritation [6.3/8.2]

Type of Study	**Acute dermal irritation – 4-hour exposure, rabbits**
Flag	Key study

Test Substance	DPX-HGW86-236; batch, E108803-5; purity, 100.4 g/L
Endpoint	Skin irritation/corrosion – Draize scores
Value	Erythema: 0.56; Oedema: 0.56 (mean of 24, 48 & 72 hour scores [Appendix 11B.2; User Guide for Thresholds and Classifications; EPA, 2012])
Reference	Finlay, C. (2006a). DPX-HGW86 100 g/L OD: Acute Dermal Irritation Study in Rabbits. DuPont Haskell Laboratories, Newark, Delaware, USA. Laboratory Project ID: DuPont-19079. Issue date 29 March 2006. Unpublished. DuPont Report No.: DuPont-19079. US MRID 48120205
Klimisch Score	1
Amendments/Deviations	None
GLP	Yes
Test Guideline/s	US EPA OPPTS 870.2500 (1998); OECD 404 (2002); EEC Method B.4 92/69/EEC (1992)
Species	Rabbit
Strain	New Zealand White
No/Sex/Group	3 Males
Dose Levels	0.5 ml
Exposure Type	Undiluted to shaved, intact skin (semi-occlusive) for 4 hours
Study Summary	Erythema (score of 1 or 2) was observed in three rabbits, and oedema (score of 1 or 3) was observed in one rabbit during the study. One rabbit also exhibited desquamation. No clinical signs of toxicity were observed, and no body weight loss occurred
Additional Comments	All irritation cleared in two rabbits by 24 hours after treatment. All dermal irritation cleared in the remaining rabbit by 8 days
Conclusion	**Cyantraniliprole (DPX-HGW86) 100 g/L OD (Benevia) should not be classified for Skin Irritation (Section 11.2.2; User Guide for Thresholds and Classifications; EPA, 2012), based on the submitted evidence (mean Draize scores less than the specified threshold)**

Eye Irritation [6.4/8.3]

Type of Study	**Acute eye irritation – unwashed, rabbits**
Flag	Key study

Test Substance	DPX-HGW86-236; batch, E108803-5; purity, 100.4 g/L
Endpoint	Eye irritation/corrosion – Draize scores
Value	0.0 for corneal opacity; 0.0 for iritis; 0.44 for conjunctival redness; 0.11 for chemosis (mean of 24, 48 & 72 hour scores [Appendix 12B.2; User Guide for Thresholds and Classifications; EPA, 2012])
Reference	Finlay, C. (2006b). DPX-HGW86 100 g/L OD: Acute Eye Irritation Study in Rabbits. DuPont Haskell Laboratories, Newark, Delaware, USA. Laboratory Project ID: DuPont-19080. Issue date 11 April 2006. Unpublished. DuPont Report No.: DuPont-19080. US MRID 48120206
Klimisch Score	1
Amendments/Deviations	None
GLP	Yes
Test Guideline/s	US EPA OPPTS 870.2400 (1998); OECD 405 (2002); EEC Method B.4 92/69/EEC (1992)
Species	Rabbit
Strain	New Zealand White
No/Sex/Group	3 Males
Dose Levels	0.1 mL
Exposure Type	Lower conjunctival sac – un-rinsed
Study Summary	Conjunctival redness (score of 1 or 2), conjunctival chemosis (score of 1 or 2), and discharge (score of 2 or 3) were observed in the treated eyes of all three rabbits. Fluorescein stain examinations were negative for corneal injury throughout the study. The treated eyes of the rabbits were normal by 24, 48, or 72 hours after instillation of the test substance. No clinical signs of toxicity were observed, and no biologically important body weight losses occurred
Additional Comments	All animals were free of ocular irritation within 72 hours
Conclusion	**Cyantraniliprole (DPX-HGW86) 100 g/L OD (Benevia) should not be classified for Eye Irritation (Section 12.2.2; User Guide for Thresholds and Classifications; EPA, 2012), based on the submitted evidence (mean Draize scores less than the specified threshold)**

Contact Sensitisation [6.5]

Type of Study	**Local lymph node assay (LLNA) in mice**

Flag	Weight of evidence
Test Substance	DPX-HGW86-236; batch, E108803-5; purity, 100.4 g/L
Endpoint	Cell proliferation in the draining auricular lymph nodes
Value	Stimulation Index, SI: 5%, 4.17; 25%, 5.47; 50%, 6.66; 100%, 6.54
Reference	Hoban, D. (2006). DPX-HGW86 100 g/L OD: Local Lymph Node Assay (LLNA) in Mice. DuPont Haskell Laboratories, Newark, Delaware, USA. Laboratory Project ID: DuPont-19081. Issue date 3 March 2006. Unpublished. DuPont Report No.: DuPont-19081. US MRID 48120207
Klimisch Score	1
Amendments/Deviations	None
GLP	Yes
Test Guideline/s	US EPA OPPTS 870.2600 (2003); OECD 429 (2001)
Species	Mouse
Strain	CBA/JHsd
No/Sex/Group	5 Females
Dose Levels	0, 5, 25, 50 or 100% (1 g/mL) in acetone:olive oil [25% hexylcinnamaldehyde in acetone:olive oil as positive control]
Exposure Type	Topical to the dorsum of each ear on 3 consecutive days
Study Summary	No statistically significant differences in mean body weights compared to the vehicle control group were observed at any test concentration. Statistically significant differences in mean body weight gains compared to the vehicle control group were observed at the 100% test concentration (decreased) and positive control (increased). All mice in the 100% test substance group were observed to have wet fur on their neck and dorsal area on test day 5. One mouse (number 1012) in the 100% test substance group also had hair loss of the head. On test day 5, the animals were co-housed prior to sacrifice. Animals 812 and 815 were observed to have all fur missing from the scalp and around the ears. Animals from group VIII were housed separately until sacrifice. Statistically significant increases in cell proliferation measurements compared to the vehicle control group were observed at all test concentrations. Stimulation indexes of greater than 3.0 were observed at all test concentrations of DPX-HGW86 100 g/L OD. Therefore, the EC3 value (the estimated concentration required to induce a threshold positive response, i.e., stimulation index = 3) for the test substance under the conditions of this study was not

	calculable. A 25% concentration of the positive control, HCA, produced a dermal sensitization response in mice (SI, 4.24). Therefore, the LLNA test system was valid for this study with DPX-HGW86 100 g/L OD
Additional Comments	A threshold positive response requires a Stimulation Index ≥ 3
Conclusion	**Cyantraniliprole (DPX-HGW86) 100 g/L OD (Benevia) should be classified 6.5B for Contact Sensitisation (positive response in an OECD test) (Section 13.2.4; User Guide for Thresholds and Classifications; EPA, 2012), based on the submitted evidence**

Type of Study	**Dermal sensitisation – Buehler Method**
Flag	Weight of evidence
Test Substance	DPX-HGW86-236; batch, E108803-5; purity, 100.4 g/L
Endpoint	Dermal sensitisation – Draize scores after challenge
Value	Erythema: 0.75 at 24 hours & 0.58 at 48 hours (mean scores)
Reference	Lowe, C. (2009). DPX-HGW86 100 g/L OD: Dermal Sensitization Test - Buehler Method. Eurofins PSL, Dayton, New Jersey, USA. Laboratory Project ID: EPSL Study No.: 22033, Revision 1. Issue date 9 January 2009. Unpublished. DuPont Report No.: DuPont-22769. US MRID 48120208
Klimisch Score	1
Amendments/Deviations	None
GLP	Yes
Test Guideline/s	US EPA OPPTS 870.2600 (2003); OECD 406 (1992)
Species	Guinea pig
Strain	Hartley albino
No/Sex/Group	20 Males
Dose Levels	Topical induction: 0.4 mL undiluted; challenge: 0.4 mL at 6% w/w in distilled water [alpha-hexylcinnamaldehyde as positive control]
Exposure Type	Topical 6-hour induction exposure on 3 consecutive weeks; topical challenge 27 days after first induction exposure
Study Summary	Very faint to faint erythema (0.5-1) was noted for all test sites during the induction phase.

	Ten of twenty test animals exhibited signs of a sensitization response (faint erythema, 1) 24 hours after challenge. Similar irritation persisted at five sites through 48 hours. Very faint erythema (0.5) was noted for all other sites after challenge. Very faint erythema (0.5) was noted for four of ten naive control sites 24 hours after challenge. Irritation persisted at two of these sites through 48 hours. Seven of ten positive control animals exhibited signs of a sensitization response (faint to moderate erythema, 1-2) 24 hours after challenge. Similar indications persisted at four sites through 48 hours. Very faint erythema (0.5) was noted for all other sites after challenge
Additional Comments	No additional comments
Conclusion	**Cyantraniliprole (DPX-HGW86) 100 g/L OD should be classified 6.5B for Contact Sensitisation (≥15% positive response with a non-adjuvant type test) (Section 13.2.2; User Guide for Thresholds and Classifications; EPA, 2012), based on the submitted evidence**

Dermal absorption

Type of Study	**Dermal absorption – *in vivo*, rats**
Flag	Supporting study
Test Substance	[PC-^{14}C]-cyantraniliprole; lot, HGW86 3562-042; radiochemical purity, 98.6% Cyantraniliprole (DPX-HGW86); batch, HGW86-307; purity, 99.2%
Endpoint	Not applicable
Value	Not applicable
Reference	Fasano, W.J. (2008a). Cyantraniliprole (DPX-HGW86) 100 g/L OD: *In Vivo* Dermal Absorption of Cyantraniliprole in the Rat. DuPont Haskell Laboratories, Newark, Delaware, USA. Laboratory Project ID: DuPont-24503. Issue date 17 December 2008. Unpublished. DuPont Report No.: DuPont-24503. US MRID 48120209
Klimisch Score	1
Amendments/Deviations	None
GLP	Yes
Test Guideline/s	OECD 427 (2004); OECD Guidance Document for the Conduct of Skin Absorption Studies (2004); EC Sanco/222/2000 rev 7 (2004)

Species	Rat
Strain	Crl:CD(SD)
No/Sex/Group	4 Males per dose / time-point
Dose Levels	Cyantraniliprole (DPX-HGW86) 100 g/L OD (Cyantraniliprole 100 g/L OD), was applied as the undiluted concentrate at 100 g Cyantraniliprole/L and as a 1 g Cyantraniliprole/L aqueous dilution. The aqueous dilution was applied at 10 µg/cm^2 per area of skin, and the undiluted concentrate was applied at 1000 µg/cm^2
Exposure Type	To shaved, intact skin (semi-occlusive) for 6 hours
Study Summary	Cyantraniliprole 100 g/L OD, 100 g Cyantraniliprole/L Undiluted Concentrate: During the 6-hour dermal exposure to the undiluted concentrate of 100 g Cyantraniliprole /L OD, only a negligible amount of the applied dose was absorbed (0.36%). At the end of the exposure phase, washing of the skin surface accounted for major portion of the applied dose (88.6%), while removal of the stratum corneum by tape stripping accounted for approximately 3.43%. Given the amount of dose absorbed (0.36%) and the dose remaining in the tape-stripped skin (0.36%), the total absorbable dose at 6 hours was calculated to be 0.72%. Based on a 498-hour post exposure recovery/collection period following the 6-hour dermal exposure (~21 days), the maximum absorbable dose was 1.36%, which suggests that only a small portion of bound skin residue associated with the stratum corneum (approximately 0.64% of 3.43%) was absorbed systemically. Cyantraniliprole 100 g/L OD, 100 g Cyantraniliprole/L Undiluted Concentrate: Over the course of a 6-hour dermal exposure to the 1 g Cyantraniliprole/L aqueous dilution of the Cyantraniliprole 100 g/L OD formulation, only a negligible amount of the applied dose was absorbed (0.18%). At the end of the exposure phase, washing of the skin surface accounted for a vast majority of the applied dose (>86%), while removal the stratum corneum by tape stripping accounted for 4.44%. Given the amount absorbed (0.18%) and the dose remaining in the tape-stripped skin (0.30%), the total absorbable dose at 6 hours was calculated to be 0.47%. Based on a 498-hour recovery/ collection period following a 6-hour dermal exposure (~21 days), the maximum absorbable dose was 0.74%, which was slightly greater, yet comparable to that observed at 6 hours post dose, which suggests that only a small portion of bound skin residue associated with the stratum corneum (approximately 0.27% of 4.44%) was absorbed systemically

Additional Comments	No additional comments
Conclusion	**Following a 6-hour dermal exposure to Cyantraniliprole 100 g/L OD formulation, when applied either as the undiluted concentrate (100 g cyantraniliprole/L or as a 1 g cyantranilirpole/L aqueous dilution, total absorption was low. Maximum absorption following a 498-hour recovery/collection period, represented as a percent of the applied dose, was slightly higher for the neat undiluted formulation (1.36%) than for the aqueous dilution (0.74%)**

Type of Study	**Dermal absorption – *in vitro*, rat and human**
Flag	Supporting study
Test Substance	[PC-^{14}C]-cyantraniliprole; lot, HGW86 3562-042; radiochemical purity, 98.6% Cyantraniliprole (DPX-HGW86); batch, HGW86-307; purity, 99.2%
Endpoint	Not applicable
Value	Not applicable
Reference	Fasano, W.J. (2008b). Cyantraniliprole (DPX-HGW86) 100 g/L OD: *In Vitro* Kinetics of Cyantraniliprole in Rat and Human Skin. DuPont Haskell Laboratories, Newark, Delaware, USA. Laboratory Project ID: DuPont-24504. Issue date 17 December 2008. Unpublished. DuPont Report No.: DuPont-24504. US MRID 48120210
Klimisch Score	1
Amendments/Deviations	None
GLP	Yes
Test Guideline/s	OECD 428 (2004); OECD Guidance Document for the Conduct of Skin Absorption Studies (2004); EC Sanco/222/2000 rev 7 (2004)
Species	Rat Human (cadaver)
Strain	Crl:CD(SD), male Caucasian, female, abdomen
No/Sex/Group	12 preparations per dose / time-point
Dose Levels	Cyantraniliprole (DPX-HGW86) 100 g/L OD (Cyantraniliprole 100 g/L OD), was applied as an undiluted concentrate at 100 g cyantraniliprole/L (at 1000 µg/cm^2) and as a 1 g cyantraniliprole/L aqueous dilution (at 10 µg/cm^2)

Exposure Type	Haskell dermal diffusion cell system – 6 hour exposure
Study Summary	Cyantraniliprole 100 g/L OD, 100 g Cyantraniliprole/L Undiluted Concentrate: Total penetration, receptor fluid only, represented 6.30% of the applied dose for rat skin; radiolabeled cyantraniliprole from the 100 g Cyantraniliprole/L OD undiluted concentrate did not penetrate through human skin into the receptor fluid over the 6-hour exposure phase. Washing of the skin at 6 hours removed >77% of the applied dose from rat skin and >88% from human skin, which represented a majority of the unabsorbed dose. At the end of the 6-hour exposure period, tape-stripping of the stratum corneum, the primary barrier to systemic uptake of chemicals via the skin, removed 7.17% and 2.18% of the applied dose from rat and human skin, respectively; of the total dose retained in the stratum corneum similar levels were contained in tapes 1 and 2 from rat skin (~77%) and human skin (~62%). The total absorbable dose at the end of the 6-hour exposure (receptor fluid plus tape-stripped skin) was approximately 42-fold greater for rat skin (10%) than for human skin (0.24%). Post-exposure, a portion of the dose contained in rat and human skin continued to partition into the receptor fluid but a reduced rate compared to the rate of penetration during the 6-hour exposure. The maximum absorbable dose 18 hours post-exposure was 10.5% and 0.25% for rat and human skin, respectively. Cyantraniliprole 100 g/L OD, 1 g Cyantraniliprole/L Aqueous Dilution: Cumulative penetration (amount per area) of cyantraniliprole from the 1 g cyantraniliprole/L aqueous dilution of the cyantraniliprole 100 g/L OD formulation at the end of the exposure was only measurable for rat skin (0.43 µg equiv/cm²) and represented 5.65% of the applied dose. Washing of the skin at the end of the 6 hour exposure removed slightly more of the applied dose from human skin (81.2%) than from rat skin (61.9%). Tape-stripping of the stratum corneum, the primary barrier to systemic uptake of chemicals via the skin, removed 23.2% and 12.1% of the applied dose from rat and human skin, respectively; of the total dose retained in the stratum corneum slightly more was contained in tapes 1 and 2 from human skin (~89%) than from rat skin (~70%). The total absorbable dose at the end of the 6-hour exposure (receptor fluid plus tape-stripped skin) was approximately 14-fold greater for rat skin (13.9%) than for human skin (1.00%).

	Post-exposure, a portion of the dose contained in rat and human skin continued to partition into the receptor fluid but a reduced rate compared to the rate of penetration during the 6-hour exposure. The maximum absorbable dose 18 hours post-exposure was 20.2% and 0.86% for rat and human skin, respectively
Additional Comments	No additional comments
Conclusion	**Using an *in vitro* dermal static diffusion cell model, the maximum absorbable dose of the undiluted concentrate 18 hours post-exposure was 10.5% and 0.25% for rat and human skin; and, and for the aqueous dilution (1%), 20.2% and 0.86%, respectively**

General conclusion about acute toxicity – Benevia

Cyantraniliprole (DPX-HGW86) 100 g/L OD (Benevia) was shown to have low acute toxicity by the oral, dermal and inhalation routes, with no adverse effects at limit doses (oral and dermal) or the maximum practicably obtainable concentration (inhalation). Therefore classification for acute toxicity is not required.

Cyantraniliprole (DPX-HGW86) 100 g/L OD (Benevia) was shown to be non-irritating to the skin and eye in standard test systems. Therefore classification for skin or eye corrosion/irritation is not required.

Cyantraniliprole (DPX-HGW86) 100 g/L OD (Benevia) was shown to be a contact sensitiser in the local lymph node assay and the Buehler guinea pig test, and should be classified 6.5B.

Dermal absorption of the concentrated formulation of Benevia (100 g cyantraniliprole/L) was 1.36% in a rat *in vivo* study, 10.5% in rat skin *in vitro* and 0.25% in human skin *in vitro*. For the aqueous dilution (1g cyantraniliprole/L), the maximum absorbable dose was 0.74% in rats *in vivo*, 20.2% in rat skin *in vitro* and 0.86% in human skin *in vitro*.

Acute toxicity and dermal absorption – Exirel

Acute Oral Toxicity [6.1 (oral)]

Type of Study	**Acute oral toxicity – up-down procedure, rat**
Flag	Weight of evidence
Test Substance	DPX-HGW86-358; batch, E112260-064; purity, 102.8 g/L
Endpoint	LD_{50}
Value	>5,000 mg/kg b.w.
Reference	Moore, G.E. (2008a). Cyantraniliprole (DPX-HGW86) 100 g/L SE: Acute Oral Toxicity - Up-and-Down Procedure in Rats. Eurofins PSL, Dayton, New Jersey,

	USA. Laboratory Project ID: EPSL Study Number: 25999. Issue date 24 October 2008. Unpublished. DuPont Report No.: DuPont-26717. US MRID 48120406
Klimisch Score	1
Amendments/Deviations	None
GLP	Yes
Test Guideline/s	US EPA OPPTS 870.1100 (2002); OECD 425 (2006)
Species	Rat
Strain	Sprague Dawley derived
No/Sex/Group	3 Females (fasted)
Dose Levels	5000 mg/kg b.w.
Exposure Type	Gavage
Study Summary	All animals survived, gained body weight, and appeared active and healthy during the study. There were no signs of gross toxicity, adverse pharmacologic effects, or abnormal behaviour. No gross abnormalities were noted for any of the animals when necropsied at the conclusion of the 14-day observation period
Additional Comments	No additional comments
Conclusion	**Cyantraniliprole (DPX-HGW86) 100 g/L SE (Exirel) should not be classified for Acute Oral Toxicity (no marked adverse effects at the limit dose of 5,000 mg/kg b.w.), based on the submitted evidence**

Type of Study	**Acute oral toxicity – up-down procedure, mice**
Flag	Weight of evidence
Test Substance	DPX-HGW86-358; batch, E112260-064; purity, 102.8 g/L
Endpoint	LD_{50}
Value	>5,000 mg/kg b.w.
Reference	Moore, G.E. (2008b). Cyantraniliprole (DPX-HGW86) 100 g/L SE: Acute Oral Toxicity - Up-and-Down Procedure in Mice. Eurofins PSL, Dayton, New Jersey, USA. Laboratory Project ID: EPSL Study Number: 26000. Issue date 24 October 2008. Unpublished. DuPont Report No.: DuPont-26795. US MRID 48120411

Klimisch Score	1
Amendments/Deviations	None
GLP	Yes
Test Guideline/s	US EPA OPPTS 870.1100 (2002); OECD 425 (2006)
Species	Mice
Strain	Sprague Dawley derived
No/Sex/Group	3 Females (fasted)
Dose Levels	5000 mg/kg b.w. (20 mL/kg b.w.)
Exposure Type	Gavage
Study Summary	All animals survived, gained body weight, and appeared active and healthy during the study. There were no signs of gross toxicity, adverse pharmacologic effects, or abnormal behaviour. No gross abnormalities were noted for any of the animals when necropsied at the conclusion of the 14-day observation period
Additional Comments	No additional comments
Conclusion	**Cyantraniliprole (DPX-HGW86) 100 g/L SE (Exirel) should not be classified for Acute Oral Toxicity (no marked adverse effects at the limit dose of 5,000 mg/kg b.w.), based on the submitted evidence**

Acute Dermal Toxicity [6.1 (dermal)]

Type of Study	**Acute dermal toxicity – rat**
Flag	Key study
Test Substance	DPX-HGW86-358; batch, E112260-064; purity, 102.8 g/L
Endpoint	LD_{50}
Value	>5,000 mg/kg b.w.
Reference	Moore, G.E. (2008d). Cyantraniliprole (DPX-HGW86) 100 g/L SE: Acute Dermal Toxicity in Rats. Eurofins PSL, Dayton, New Jersey, USA. Laboratory Project ID: EPSL Study Number: 26001. Issue date 24 October 2008. Unpublished. DuPont Report No.: DuPont-26718. US MRID 48120407

Klimisch Score	1
Amendments/Deviations	None
GLP	Yes
Test Guideline/s	U.S. EPA OPPTS 870.1200 (1998); OECD 402 (1987)
Species	Rat
Strain	Sprague Dawley derived
No/Sex/Group	5
Dose Levels	5000 mg/kg b.w.
Exposure Type	To shaved, intact skin (semi-occlusive) for 24 hours
Study Summary	All animals survived and gained body weight over the course of the study. Apart from the dermal irritation noted on the dose site of all animals during the 14-day observation period, there were no other clinical findings recorded for any animal over the course of the study. No gross abnormalities were noted for any of the animals when necropsied at the conclusion of the 14-day observation period
Additional Comments	No additional comments
Conclusion	**Cyantraniliprole (DPX-HGW86) 100 g/L SE (Exirel) should not be classified for Acute Dermal Toxicity (no marked adverse effects at the limit dose of 5,000 mg/kg b.w.), based on the submitted evidence**

Acute Inhalation Toxicity [6.1 (inhalation)]

Type of Study	**Acute inhalation toxicity – nose only; single 4-hour exposure; aerosol, rats**
Flag	Key study
Test Substance	DPX-HGW86-358; batch, E112260-064; purity, 102.8 g/L
Endpoint	LC_{50}
Value	>2.4 mg/L
Reference	Kegelman, T.A. (2009a). Cyantraniliprole (DPX-HGW86) 100 g/L SE: Inhalation Median Lethal Concentration (LC_{50}) Study in Rats. DuPont Haskell Laboratories, Newark, Delaware, USA. Laboratory Project ID: DuPont-26579. Issue date 2

	April 2009. Unpublished. DuPont Report No.: DuPont-26579. US MRID 48120405
Klimisch Score	1
Amendments/Deviations	None considered significant
GLP	Yes
Test Guideline/s	US EPA OPPTS 870.1300 (1998); OECD 403 (1981); EEC Method B.2 92/69/EEC (1992)
Species	Rat
Strain	Crl:CD(SD)IGS
No/Sex/Group	5
Dose Levels	2.4 ± 0.14 mg/L aerosol; mean mass median aerodynamic diameter (MMAD) (± geometric standard deviation [GSD]), 5.8 ± 2.2 µm
Exposure Type	Nose only
Study summary	No mortalities were observed in either exposure group. Transient weight losses were observed in 2 of 5 male rats on post-exposure day 1 and in one female rat on post-exposure day 2. Discharge from the eyes and nose was observed in all animals immediately following exposure, which resolved by the next day. Nasal and ocular discharge is commonly observed in rats following nose-only exposures
Additional Comments	Difficulties were encountered generating a 5.0 mg/L exposure atmosphere due to the test substance's tendency to stick and adhere to the exposure chamber surfaces. The conditions used to generate the 2.4 mg/L exposure were optimized to generate the highest airborne concentration of the test substance and, therefore, represents the maximum practically-attainable atmospheric aerosol concentration
Conclusion	**Cyantraniliprole (DPX-HGW86) 100 g/L SE should not be classified for Acute Inhalation Toxicity (no marked adverse effects at 2.4 mg/L, the maximum attainable concentration), based on the submitted evidence**

Skin Irritation [6.3/8.2]

Type of Study	**Acute dermal irritation – 4-hour exposure, rabbits**
Flag	Key study
Test Substance	DPX-HGW86-358; batch, E112260-064; purity, 102.8 g/L

Endpoint	Skin irritation/corrosion – Draize scores
Value	Erythema: 1.67; Oedema: 1.44 (mean of 24, 48 & 72 hour scores [Appendix 11B.2; User Guide for Thresholds and Classifications; EPA, 2012])
Reference	Durando, J. (2008a). Cyantraniliprole (DPX-HGW86) 100 g/L SE: Primary Skin Irritation in Rabbits. Eurofins PSL, Dayton, New Jersey, USA. Laboratory Project ID: EPSL Study Number: 26003. Issue date 9 December 2008. Unpublished. DuPont Report No.: DuPont-26721. US MRID 48120409
Klimisch Score	1
Amendments/Deviations	None
GLP	Yes
Test Guideline/s	US EPA OPPTS 870.2500 (1998); OECD 404 (2002)
Species	Rabbit
Strain	New Zealand White
No/Sex/Group	3 Females
Dose Levels	0.5 ml
Exposure Type	Undiluted to shaved, intact skin (semi-occlusive) for 4 hours
Study Summary	Very slight to well-defined erythema and very slight to slight oedema were noted for all three treated dose sites. Hyperkeratosis, which is considered to be a severe dermal effect, was noted at one dose site on Day 7 and desquamation was evident at all three sites between Days 7 and 14
Additional Comments	Although dermal irritation cleared from one treated site by Day 14, very slight erythema (score, 1) and desquamation persisted in two animals through to study termination (Day 14)
Conclusion	**Cyantraniliprole (DPX-HGW86) 100 g/L SE (Exirel) should be classified 6.3A for Skin Irritation (erythema and desquamation persisting beyond 14 days) (Section 11.2.2; User Guide for Thresholds and Classifications; EPA, 2012), based on the submitted evidence**

Eye Irritation [6.4/8.3]

Type of Study	**Acute eye irritation – unwashed, rabbits**
Flag	Key study
Test Substance	DPX-HGW86-358; batch, E112260-064; purity, 102.8 g/L

Endpoint	Eye irritation/corrosion – Draize scores
Value	0.0 for corneal opacity; 0.22 for iritis; 0.67 for conjunctival redness; 0.11 for chemosis (mean of 24, 48 & 72 hour scores [Appendix 12B.2; User Guide for Thresholds and Classifications; EPA, 2012])
Reference	Durando, J. (2008b). Cyantraniliprole (DPX-HGW86) 100 g/L SE: Primary Eye Irritation in Rabbits. Eurofins PSL, Dayton, New Jersey, USA. Laboratory Project ID: EPSL Study Number: 26002. Issue date 2 December 2008. Unpublished. DuPont Report No.: DuPont-26720. US MRID 48120408
Klimisch Score	1
Amendments/Deviations	None
GLP	Yes
Test Guideline/s	US EPA OPPTS 870.2400 (1998); OECD 405 (2002)
Species	Rabbit
Strain	New Zealand White
No/Sex/Group	2 Males & 1 Female
Dose Levels	0.1 mL
Exposure Type	Lower conjunctival sac – un-rinsed
Study Summary	There was no corneal opacity noted in any treated eye during the study. One hour after test substance instillation, two treated eyes exhibited iritis and conjunctivitis was evident in all three treated eyes. The overall incidence and severity of irritation decreased with time
Additional Comments	All animals were free of ocular irritation within 72 hours
Conclusion	**Cyantraniliprole (DPX-HGW86) 100 g/L SE (Exirel) should not be classified for Eye Irritation (Section 12.2.2; User Guide for Thresholds and Classifications; EPA, 2012), based on the submitted evidence from this study (mean Draize scores less than the specified threshold)**

Contact Sensitisation [6.5]

Type of Study	**Dermal sensitisation – Buehler Method**
Flag	Key study
Test Substance	Cyantraniliprole tech.; batch, DPX-HGW86-648; purity, 95.6%
Endpoint	Dermal sensitisation – Draize scores after challenge

Value	Erythema: 0.70 at 24 hours & 0.45 at 48 hours (mean scores)
Reference	Durando, J. (2008c). Cyantraniliprole (DPX-HGW86) 100 g/L SE: Dermal Sensitization Test - Buehler Method. Eurofins PSL, Dayton, New Jersey, USA. Laboratory Project ID: EPSL Study No.: 26004. Issue date 13 November 2008. Unpublished. DuPont Report No.: DuPont-26791. US MRID 48120410
Klimisch Score	1
Amendments/Deviations	None significant
GLP	Yes
Test Guideline/s	US EPA OPPTS 870.2600 (2003); OECD 406 (1992)
Species	Guinea pig
Strain	Hartley albino
No/Sex/Group	20 Males
Dose Levels	Topical induction: 0.4 mL undiluted; challenge: 0.4 mL at 75% w/w in distilled water [alpha-hexylcinnamaldehyde as positive control]
Exposure Type	Topical 6-hour induction exposure on 3 consecutive weeks; topical challenge 27 days after first induction exposure
Study Summary	Very faint to faint erythema (0.5-1) was noted for most test sites during the induction phase. Nine of twenty test animals exhibited signs of a sensitization response (faint erythema) 24 hours after challenge. Similar irritation persisted at six sites through 48 hours. Very faint erythema (0.5) was noted for most other sites after challenge. Very faint erythema (0.5) was noted for four of ten naive control sites 24 hours after challenge. Irritation cleared from all affected sites by 48 hours. Four of ten positive control animals exhibited signs of a sensitization response (faint erythema) 24 hours after challenge. Similar indications persisted at two sites through 48 hours
Additional Comments	No additional comments
Conclusion	**Cyantraniliprole (DPX-HGW86) 100 g/L SE (Exirel) should be classified 6.5B for Contact Sensitisation (≥15% positive response with a non-adjuvant type test) (Section 13.2.2; User Guide for Thresholds and Classifications; EPA, 2012), based on the submitted evidence**

Dermal absorption

Type of Study	**Dermal absorption – *in vivo*, rats**
Flag	Supporting study
Test Substance	[PC-^{14}C]-cyantraniliprole; lot, HGW86 3562-042; radiochemical purity, 98.6% Cyantraniliprole (DPX-HGW86); batch, HGW86-307; purity, 99.2%
Endpoint	Not applicable
Value	Not applicable
Reference	Fasano, W.J. (2009a). Cyantraniliprole (DPX-HGW86) 100 g/L SE: *In vivo* Dermal Absorption of Cyantraniliprole in the Rat. DuPont Haskell Laboratories, Newark, Delaware, USA. Laboratory Project ID: DuPont-27074. Issue date 15 May 2009. Unpublished. DuPont Report No.: DuPont-27074. US MRID 48120413
Klimisch Score	1
Amendments/Deviations	None
GLP	Yes
Test Guideline/s	OECD 427 (2004); OECD Guidance Document for the Conduct of Skin Absorption Studies (2004); EC Sanco/222/2000 rev 7 (2004)
Species	Rat
Strain	Crl:CD(SD)
No/Sex/Group	4 Males per dose / time-point
Dose Levels	Cyantraniliprole (DPX-HGW86) 100 g/L SE (Cyantraniliprole 100 g/L SE) applied as the undiluted concentrate at 100 g Cyantraniliprole/L and as a 1 g Cyantraniliprole/L aqueous dilution at 1000 µg/cm^2 and 10 µg/cm^2 respectively
Exposure Type	To shaved, intact skin (semi-occlusive) for 6 hours
Study Summary	Cyantraniliprole 100 g/L SE, 100 g Cyantraniliprole/L Undiluted Concentrate: During the 6-hour dermal exposure to the undiluted concentrate of Cyantraniliprole 100 g/L SE, only a minor amount of the applied dose was absorbed (0.73%). At the end of the exposure phase, washing of the skin surface accounted for major portion of the applied dose (>86%), while removal of the stratum corneum by tape stripping accounted for approximately 2.17%. Given the amount of dose absorbed (0.73%) and the dose remaining in the tape-stripped skin (0.37%), the total absorbable dose at 6 hours was calculated to be 1.10%. Based on a 498-hour post exposure recovery/collection period

	following the 6-hour dermal exposure (~21 days), the maximum absorbable dose was 1.25% Cyantraniliprole 100 g/L SE, 1 g Cyantraniliprole/L Aqueous Dilution: Over the course of a 6-hour dermal exposure to the 1 g Cyantraniliprole/L aqueous dilution of the Cyantraniliprole 100 g/L SE formulation, only a minor amount of the applied dose was absorbed (0.42%). At the end of the exposure phase, washing of the skin surface accounted for a vast majority of the applied dose (>96%), while removal the stratum corneum by tape stripping accounted for 2.61%. Given the amount absorbed (0.42%) and the dose remaining in the tape-stripped skin (0.23%), the total absorbable dose at 6 hours was calculated to be 0.64%. Based on a 498-hour recovery/collection period following a 6-hour dermal exposure (~21 days), the maximum absorbable dose was 1.47%
Additional Comments	No additional comments
Conclusion	**Following a 6-hour dermal exposure to Cyantraniliprole 100 g/L SE formulation (Benevia), when applied either as the undiluted concentrate or as an aqueous dilution, total absorption was low. Maximum absorption, following a 498-hour recovery/collection period, represented as a percent of the applied dose, was higher for the aqueous dilution (1.47%) than for neat undiluted formulation (1.25%)**

Type of Study	**Dermal absorption – *in vitro*, rat and human**
Flag	Supporting study
Test Substance	[PC-^{14}C]-cyantraniliprole; lot, HGW86 3562-042; radiochemical purity, 98.6% Cyantraniliprole (DPX-HGW86); batch,HGW86-307; purity, 99.2%
Endpoint	Not applicable
Value	Not applicable
Reference	Fasano, W.J. (2009b). Cyantraniliprole (DPX-HGW86) 100 g/L SE: *In Vitro* Kinetics of Cyantraniliprole in Rat and Human Skin. DuPont Haskell Laboratories, Newark, Delaware, USA. Laboratory Project ID: DuPont-27073. Issue date 15 May 2009. Unpublished. DuPont Report No.: DuPont-27073. US MRID 48120412
Klimisch Score	1
Amendments/Deviations	None

GLP	Yes
Test Guideline/s	OECD 428 (2004); OECD Guidance Document for the Conduct of Skin Absorption Studies (2004); EC Sanco/222/2000 rev 7 (2004)
Species	Rat Human (cadaver)
Strain	Crl:CD(SD), male Caucasian, female, abdomen
No/Sex/Group	12 preparations per dose / time-point
Dose Levels	Cyantraniliprole (DPX-HGW86) 100 g/L SE (Cyantraniliprole 100 g/L SE) was applied as the undiluted concentrate at 100 g cyantraniliprole/L and as a 1 g cyantraniliprole/L aqueous dilution at 1000 µg/cm^2 and 10 µg/cm^2 respectively
Exposure Type	Haskell dermal diffusion cell system – 6 hour exposure
Study Summary	Cyantraniliprole 100 g/L SE, 100 g Cyantraniliprole/L Undiluted Concentrate: Total penetration, receptor fluid only, represented 6.90% of the applied dose for rat skin; radiolabeled cyantraniliprole from the Cyantraniliprole 100 g/L SE undiluted concentrate did not penetrate through human skin into the receptor fluid over the 6-hour exposure phase. Washing of the skin at 6 hours removed >81% of the applied dose from rat skin and >93% from human skin, which represented a majority of the unabsorbed dose At the end of the 6-hour exposure period, tape-stripping of the stratum corneum, the primary barrier to systemic uptake of chemicals via the skin, removed 1.63% and 0.55% of the applied dose from rat and human skin, respectively; of the total dose retained in the stratum corneum similar levels were contained in tapes 1 and 2 from rat skin (~53%) and human skin (~52%) The total absorbable dose at the end of the 6-hour exposure (receptor fluid plus tape-stripped skin) was approximately 10.1-fold greater for rat skin (9.41%) than for human skin (0.93%) Post-exposure, a portion of the dose contained in rat and human skin continued to partition into the receptor fluid but at a reduced rate compared to the rate of penetration during the 6-hour exposure The maximum absorbable dose 18 hours post-exposure was 13.4% and 2.70% for rat and human skin, respectively

	Cyantraniliprole 100 g/L SE, 1 g Cyantraniliprole/L Aqueous Dilution: Cumulative penetration (amount per area) at the end of the exposure was only measurable for rat skin (0.14 µg equiv/cm²) and represented 1.61% of the applied dose. Washing of the skin at the end of the 6 hour exposure removed 77% of the applied dose from rat skin and 71% from human skin Tape-stripping of the stratum corneum, the primary barrier to systemic uptake of chemicals via the skin, removed 13.1% and 11.8% of the applied dose from rat and human skin, respectively; of the total dose retained in the stratum corneum slightly more was contained in tapes 1 and 2 from human skin (~75%) than from rat skin (~65%) The total absorbable dose at the end of the 6-hour exposure (receptor fluid plus tape-stripped skin) was approximately 2.5-fold greater for rat skin (8.40%) than for human skin (3.33%) Post-exposure, a portion of the dose contained in rat and human skin continued to partition into the receptor fluid The maximum absorbable dose 18 hours post-exposure was 10.7% and 6.07% for rat and human skin, respectively
Additional Comments	No additional comments
Conclusion	**Using an *in vitro* dermal static diffusion cell model, the maximum absorbable dose of the undiluted concentrate 18 hours post-exposure was 13.4% and 2.70% for rat and human skin, respectively; and for the aqueous dilution, 10.7% and 6.07%, respectively**

General conclusion about acute toxicity – Exirel

Cyantraniliprole (DPX-HGW86) 100 g/L SE (Exirel) was shown to have low acute toxicity by the oral, dermal and inhalation routes, with no adverse effects at limit doses (oral and dermal) or the maximum practicably obtainable concentration (inhalation). Therefore classification for acute toxicity is not required.

Cyantraniliprole (DPX-HGW86) 100 g/L SE (Exirel) was shown to be irritating to the skin and should be classified 6.3A. It was non-irritating to the eye in standard test systems and therefore classification for eye irritation is not required.

Cyantraniliprole (DPX-HGW86) 100 g/L SE (Exirel) was shown to be a contact sensitiser in a non-adjuvant test system after a challenge with 75% w/w, and should be classified 6.5B.

Dermal absorption of the concentrated formulation of Exirel (100 g cyantraniliprole/L) was 1.25% in a rat *in vivo* study, 13.4% in rat skin *in vitro* and 2.7% in human skin *in vitro*. For the aqueous dilution (1g

cyantraniliprole/L), the maximum absorbable dose was 1.47% in rats in vivo, 10.7% in rat skin *in vitro* and 6.07% in human skin *in vitro*.

Environmental fate - for the active ingredient and metabolite(s)

Unless otherwise noted, all studies were conducted according to GLP and were fully compliant with all requirements of the standard international test methods used. All data for cyantraniliprole, its metabolites and the formulations Benevia and Exirel were sourced from the draft OECD Joint Review Monograph Annex B.8 Fate and behaviour (March 2012) unless otherwise stated.

Degradation and fate in soils

Route of degradation in soil

The laboratory studies were performed with a radioactive labelling in 2 positions of the active ingredient molecule: the cyano group [CN-^{14}C]-cyantraniliprole and pyrazole carbonyl [PC-^{14}C]-cyantraniliprole group. The results can be summarised as follows:

Overall route of degradation of cyantraniliprole was derived from a combination of aerobic soil degradation and anaerobic soil degradation as well as photolysis in moist soil. The degradation process is quite complex and proceeds along at least two major pathways in dark soil and via a combination of aerobic soil degradation as well as photodegradation in moist soil. The degradation pathways will be referred to as the IN-J9Z38 pathway, IN-JCZ38 pathway, and the photodegradation pathway, in this discussion of degradation processes.

Degradation of cyantraniliprole in dark aerobic soil proceeded along two pathways, the IN-J9Z38 pathway and the IN-JCZ38 pathway.

Formation of CO_2 indicated that the parent compound can be mineralized (up to 11.8% of CO_2 in aerobic studies but not significant in anaerobic studies). Characterization of non-extractable residue also showed significant portion of the material associated with humic and fulvic acid fractions, which infers that small molecules formed may become a part of soil organic matter (up to 22.4% of CO_2 in aerobic studies and around 5-6% in anaerobic studies).

Degradation in anaerobic soil followed the same degradation route, as seen in the aerobic soil. However, a major difference was that the IN-JCZ38 pathway became prominently less significant, since IN-JCZ38 or its succeeding degradation products (IN-JSE76 and IN-K5A79, IN-PLT97) were either not detectable or were found in very low proportions. Evidently, lack of oxygen has a significant impact on the degradation route termed as the IN-JCZ38 pathway. Overall degradation rate, however, was not diminished since the lack of degradation along IN-JCZ38 pathway was compensated by increased contribution from the IN-J9Z38 pathway. The same behaviour was also noted in the sterile soil, which demonstrates the important role of the physic-chemical reactions (i.e.hydrolysis) in the degradation of cyantraniliprole. In sterile soil, IN-J9Z38 pathway was the primary degradation process in operation.

Degradation in soil under photolysis conditions is clearly mediated by the moisture content of the soil. In soil, which was moist at the start but not maintained moist, the only degradation product observed was IN-J9Z38, which formed due to hydrolytic degradation in soil.

However, when soil was maintained in a moist condition, the aqueous photolysis products were also formed in soil. IN-NXX70 and IN-QKV54 are significant aqueous photolysis products, and they were both observed in identifiable quantities in moist soil (max 4.8% and 17.2% respectively). An additional metabolite, IN-RNU71, was also identified and it was formed from photolysis of IN-J9Z38.

An overall degradation pathway for degradation of cyantraniliprole in soil under all conditions is displayed in Figure on next page.

The highest percent of each significant degradate formed in any of the soil degradation studies of cyantraniliprole are noted in Table 6.

Based on the metabolite proportions found in all route of degradation studies in soil, it was concluded that there were seven significant soil degradation products, which are IN-J9Z38, IN-JCZ38, IN-JSE76, IN-K5A77, IN K5A78, IN-K5A79, and IN-PLT97. All of these metabolites were monitored in all field soil dissipation studies.

In addition, it was clear that if soil was moist and had simultaneous exposure to light, some photodegradation resulting in the formation of IN-RNU71 and IN-QKV54 could take place. IN-NXX70 was an additional minor transformation product of cyantraniliprole, approaching 5% of the total residue. Therefore, these three photodegradation products were also monitored in a number of the field studies.

Overall degradation pathway for cyantraniliprole in soil

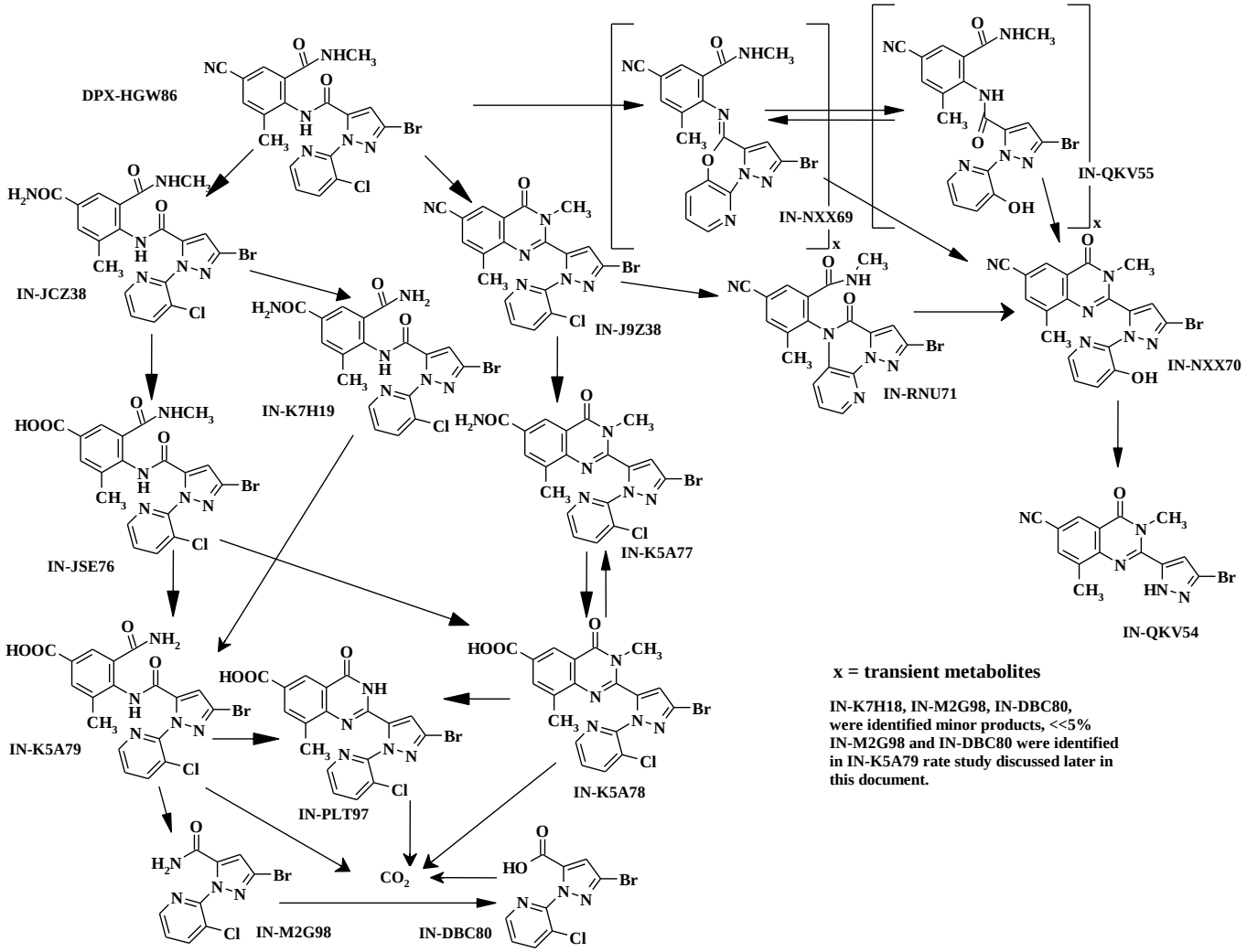


Table 9 Maximum percent formation of significant metabolites in soil

Metabolite	Maximum % in aerobic soil	Maximum % in anaerobic soil	Maximum % in soil photolysis
IN-J9Z38	19.39	**71.9**	54.8
IN-JCZ38	**39.6**	5.3	3.35
IN-JSE76	**42.9**	5.8	4.2
IN-K5A77	8.9	**9.97**	1.95
IN-K5A78	**28.8**	16.2	—[a]
IN-K5A79	**9.3**	—[a]	2.97
IN-PLT97	**26.3**	—[a]	—[a]
IN-NXX70	—[a]	—[a]	4.8
IN-RNU71	—[a]	—[a]	**14.1**
IN-QKV54	—[a]	—[a]	**17.2**

Note: Maximum % is the highest found for any replicate soil sample from two labels and five soils at any sampling interval (Significant metabolites % in bold font)

[a] Not found in identifiable amounts in this system

Rate of degradation in soil

The active ingredient and all significant metabolites, which accounted for either 10% of total residues, or those which exceeded 5% at multiple sampling intervals in cyantraniliprole dosed studies, were investigated for their rate of degradation.

Table 10 Degradation rates in soil under laboratory conditions

Test type	Test substance							
	Cyantraniliprole	IN-JCZ38	IN-JSE76	IN-K5A79	IN-J9Z38	IN-K5A77	IN-K5A78	IN-PLT97
Aerobic half-life in soil (DT_{50lab}) (days)								
Gr-Ums – silt loam	43.7	133	108	23.2	90.5	161	-	640
Lleida – silty clay loam	20.9	25.5	129	40.5	78.9	42	405	293

Test type	Test substance							
	Cyantraniliprole	IN-JCZ38	IN-JSE76	IN-K5A79	IN-J9Z38	IN-K5A77	IN-K5A78	IN-PLT97
Nambs – sandy loam	8.7	14.8	43.2	37.6	224	74.1	-	236
Sassafras – sandy loam	91.9	-	108	116	50.9	-	240	70.8
Tama – silty clay loam	39.2	37	120	-	610	109	-	69.6
Anaerobic degradation in soil (DT_{50lab}) (days)	Nambs – sandy loam 4.36							
Soil photolysis half-life (DT_{50}) (days)	84							

In addition, some field studies were performed with cyantraniliprole in the USA and in Europe. The Geometrical mean of the normalised DT50 is 32.4 days.

Table 11 Degradation rates in soil under field conditions

Location	Field dissipation studies		
	Soil type	pH	Normalised DT50 (days)
Grant County, Washington, USA	Sandy loam	7.44	31.4
Porterville California, USA	Sandy Loam	7.81	20.9
Shelby County, Missouri, USA	Silt loam	6.2	50.8
Raymondville, Texas, USA	Sandy clay loam	7.9	22.9
Portage La Prairie, Manitoba, Canada	Clay loam	7.8	38.5
Nambsheim, France	Clay loam	7.93	16.9
Sevilla, Spain	Loamy sand	8.22	31.5
Goch, Germany	Silt loam	6.3	46.7
Milan, (Lodi) Italy	Loam	6	33.8
North Rose, New York, USA	Loamy sand	6.5	51.3

Overall conclusions on degradation in soil

- Cyantraniliprole displayed the same route of degradation under aerobic and anaerobic soil degradations conditions, because the degradation is mainly driven by physico-chemical reactions.
- There was no meaningful effect, clay content, or other soil properties on the rate or route of degradation in soil. The pH effect on DT50 of cyantraniliprole observed in the laboratory studies was less pronounced under field conditions.
- Degradation of cyantraniliprole was faster under anaerobic conditions.
- Some degradation of cyantraniliprole can be anticipated on soil via photolysis, if soil is moist, but no photodegradation is expected in dry soil.

- All metabolites generated continue to degrade. All soil components, with the only exception of IN-QKV54, generated some CO_2, demonstrating mineralization during the study periods.
- Nine metabolites (IN-J9Z38, IN-JCZ38, IN-JSE76, IN-K5A77, IN-K5A78, IN-K5A79, IN-PLT97, IN QKV54, and IN-RNU71) were judged to be significant, to be addressed for persistence, environmental modelling, ecological risk, and water contamination concerns.
-

Degradation and fate in aquatic systems under laboratory conditions

Table 12 Degradation and fate in aquatic environments

Test type	Test substance			
	Active	Metabolites		
	Cyantraniliprole	**IN-NXX69**	**IN-QKV54**	**IN-J9Z38**
Ready biodegradation	Not readily degradable (25.6% CO_2 evolution)			
Aqueous photolysis half-life (DT_{50}) (days)	0.22 natural water IN-NXX69 max 53% INQKV54 max 85%	0.63	28	
Degradation in aerobic water/sediment (DT_{50}), in dark conditions at 20°C (days)	Loamy sand pH 6.1 (water): **whole system 25.1** Silt loam pH 7.6 (water): whole system 3.9 IN-J9Z38 max 41.8% in water after 9 days; max 77% in sediment after 56 days. Non extractable residues in sediments: max 13.5% after 70 days			Loamy sand pH 6.1 (water): whole system 155 Silt loam pH 7.6 (water): whole system 272
Degradation in aerobic water/sediment (DT_{50}), in natural sunlight at 20°C (days)	Sand pH 7.2 (water): whole system 4.5 Silt loam pH 7.9 (water): whole system 3.6			
Degradation in anaerobic water/sediment (DT_{50}), in dark conditions at 20°C (days)	Loamy sand pH 6.6 (water): whole system 11.39 Sandy loam pH 7.8 (water): whole system 2.1			

Test type	Test substance			
	Active	Metabolites		
	Cyantraniliprole	IN-NXX69	IN-QKV54	IN-J9Z38
Water solubility at 20°C [mg/L]	14.24			
Hydrolysis half-life at 20°C (DT_{50}) (days)	pH 4 261 pH 7 61 pH 9 1.77			

In bold: value used for the risk assessment

- Degradation in aerobic water sediment systems is generally more rapid than the degradations in soil. A total system DT50 of 25 days in aerobic sandy sediment and 3.87 days in aerobic silty sediment for cyantraniliprole, exemplifies the rapid rate of degradation.
- In dark conditions, the degradation in aerobic sediments proceeded along the same pathway that was identified for soil, although the IN-J9Z38 pathway appeared to be operational predominantly while the IN-JCZ38 pathway was always minor in all systems.
- Degradation in the water sediment systems was not affected by pH as prominently, except for degradation in the water phase.
- Degradation in water alone (hydrolysis study) was clearly pH dependent, and degradation was much faster at pH 9.
- Hydrolytic degradations via the IN J9Z38 pathway appeared to be dominant. This happened even in flooded sterile soil system, whereby IN-J9Z38 was the main metabolite. Moreover, IN J9Z38 also showed further degradation (probably hydrolytic) in sterile soil as well, although at somewhat slower pace than the corresponding viable system.
- Degradation in anaerobic water sediment systems was also rapid, as indicated by shorter DT50's of 2.1 days and 11.9 days in the total systems. Degradation in anaerobic conditions also proceeded primarily via the IN-J9Z38 pathway, which is mainly driven by physico-chemical reactions.
- Photochemical degradation of cyantraniliprole in water was very rapid, as indicated by a DT50 of less than 1 day. Photolysis in water, however, showed an entirely different pathway for degradation. Degradation proceeded via an initial interim metabolite, IN-NXX69 (stable only in acidic buffer), which readily undergoes additional transformations to IN-NXX70 and IN-QKV54. Formation of numerous metabolites, observed only under aqueous photolysis conditions, underlines a rapid degradation in the presence both water and light, especially when they are available concurrently.
- Photochemical degradation in natural water is just as fast as the water solutions containing buffers only. .
- The outdoor water sediment study exemplified the comprehensive degradation of cyantraniliprole in aquatic systems in the presence of natural sunlight. The outdoor study showed that cyantraniliprole will degrade faster in the water sediment systems presence of light, and will likely degrade faster in the water sediment systems exposed to light than either degradation in dark or water alone.

- Participation of photochemical degradation pathway in degradation was analysed in the field dissipation studies as well, by analysis of IN-NXX70, IN-QKV54 and IN-RNU71. However, the photochemical degradation was only a minor degradation mechanism [<<5%] in the field because, occurrence of an overwhelming amount of water and light simultaneously is not common in the real field situations.

Route and rate of degradation in air

- Direct photolysis in top layer of aqueous system [GC Solar method]: The air concentration expected to be negligible due to low vapour pressure. The DT50 at latitude 40° is 0.23 days and 0.76 days in summer and in winter respectively.
- Photochemical oxidative degradation in air (DT_{50}): DT_{50} of 8 hours derived by the Atkinson model (version 1988).
- Volatilisation (Lyman method): The calculated volatilisation from plant surfaces and from soil is <0.001% after 24 hours.

Residues requiring further assessment

Environmental occurring metabolites requiring further assessment by other disciplines (toxicology and ecotoxicology):

- Soil: Cyantraniliprole, IN-J9Z38, IN-JCZ38, IN-JSE76, IN-K5A77, IN-K5A78, IN-K5A79, IN-PLT97, IN-QKV54, IN-RNU71 and IN-M2G98
- Surface water: Cyantraniliprole, IN-J9Z38, IN-JCZ38, IN-JSE76, IN-K5A77, IN-K5A78, IN-K5A79, IN-PLT97, IN-QKV54, IN-RNU71, IN-NXX70 and IN-M2G98
- Sediment: Cyantraniliprole, IN-J9Z38, IN-JCZ38, IN-JSE76, IN-K5A77, IN-K5A78, IN-K5A79, IN-PLT97, IN-QKV54, IN-RNU71, IN-NXX70 and IN-M2G98
- Groundwater:- Cyantraniliprole, IN-J9Z38, IN-JCZ39, IN-JSE76, IN-K5A77, IN-K5A78, IN-K5A79, IN-PLT97, IN-QKV54, IN-RNU71, IN-NXX70 and IN-M2G98
- Air: Cyantraniliprole

Mobility in soils

Batch adsorption studies were conducted with cyantraniliprole and a number of metabolites on five soils. The soils were all collected from the same locations in the USA and Europe, but were sampled in 2005, 2007 or 2009 and the soil properties such as %OC and soil pH ($CaCl_2$) changed during the 2005 – 2009 time period.

Adsorption was correlated with organic carbon content of the soils (generally higher adsorption with higher organic carbon content), however, other correlations with for example soil pH were not evident for any of the test compounds with the exception of IN-K5A79 (see table 10).

According to the FAO scale, cyantraniliprole and the metabolites IN-JCZ38 and IN-RNU71 are considered to be moderately mobile in soil, IN-J9Z38, IN-K5A77, IN-K5A78 and IN-PLT97 are slightly mobile, IN-JSE76 and IN-K5A79 are mobile and IN-QKV54 is hardly mobile.

Cyantraniliprole and all the tested metabolites desorption was less than 70%, indicating that adsorption may not be completely reversible.

No further study on the mobility in soil was conducted; the potential to contaminate groundwater was evaluated with the FOCUS model. The conclusions cannot be extrapolated to New Zealand.

Table 13 Adsorption (Kd and Koc in mL/g) on soil under laboratory conditions (batch equilibrium)

Test type		Test substance									
		Cyantraniliprole	IN-JCZ38	IN-JSE76	IN-K5A79	IN-J9Z38	IN-K5A77	IN-K5A78	IN-PLT97	IN-QKV54	IN-RNU71
Gr-Ums – silt loam	Kd	**2.77**	2.4	0.27	0.46	82	75.91	9.56	18.42	154.88	2.12
	Koc	251	218	25	42	7475	6901	869	1675	11063	152
Lleida – silty clay loam	Kd	2.81	2.58	0.25	0.49	83	93.51	7.96	15.65	191.67	1.77
	Koc	176	161	16	24	5158	5845	497	978	11275	104
Nambs – sandy loam	Kd	2.51	1.99	0.21	0.43	72	59.32	6.60	11.21	186.89	2.47
	Koc	157	124	14	26	4528	3707	412	701	9345	124
Sassafras – sandy loam	Kd	3.40	2.92	0.39	0.98	110	88.11	12.82	25.69	68.57	1.45
	Koc	243	209	28	85	7887	6294	916	1835	8571	181
Tama – silty clay loam	Kd	7.14	9.15	1.24	1.47	352	480.82	48.35	95.54	1061	5.65
	Koc	376	482	65	55	18537	25306	2545	5029	32152	171

In bold: value used for the risk assessment

Bioaccumulation

The bioaccumulation study performed with the active ingredient and the screening tests performed with the relevant metabolites (see table below) do not demonstrate any potential of bioaccumulation for any of the tested compounds.

Table 14 Bioaccumulation potential

Test type	Test substance	
	Cyantraniliprole	Metabolites
Partition coefficient octanol/water [Log Kow]	1.94 (not pH dependent)	The partition coefficients (n-octanol/water) of several soil transformation products of cyantraniliprole were determined by (HPLC): Metab. Average (Log K_{ow}) IN-J9Z38 2.8 IN-JCZ38 1.3 IN-JSE76 1.7 IN-K5A77 2.1 IN-K5A78 2.6 IN-K5A79 1.5 IN-K7H19 1.1 IN-PLT97 2.6 The partition coefficients (n-octanol/water) of three photodegradation products of cyantraniliprole were determined by HPLC: Metab. Average (Log K_{ow}) IN-NXX70 2.59 IN-RNU71 1.52 IN-QKV54 2.92
Fish bioconcentration (whole fish)	The whole-fish, steady-state bioconcentration factors of cyantraniliprole in the bluegill sunfish at mean measured concentrations of 9.41 and 93.8 µg/L were less than 1. These bioconcentration factors indicate that cyantraniliprole does not bioconcentrate in fish	

Classifications of cyantraniliprole and its metabolites for degradability and bioaccumulation potentials

Cyantraniliprole **is not rapidly degradable in the aquatic environment**, (<60% CO_2 evolution in 28 days ; DT50 in whole water sediment system >16 days) and is not considered bioaccumulative ($BCF_{whole\ fish}$ <500).

The IN-J9Z38 metabolite of cyantraniliprole has half-lives ($DT_{50\ whole\ system}$) of 155 and 272 days and is not bioccumulative.

In soil cyantraniliprole has half-life values in the range 8.7 – 91.9 days. In general,-the metabolites are more persistent than the parent.

9.6. Ecotoxicity of the active ingredient(s) and metabolite(s) and formulated product

Unless otherwise noted, all studies were conducted according to GLP and were fully compliant with all requirements of the standard international test methods used. All data for cyantraniliprole, its metabolites and the formulated products Benevia and Exirel were sourced from the draft OECD Joint Review Monograph Annex B.9 Ecotoxicology (March 2012) unless otherwise stated.

Endpoints used for classification and/or risk assessment are shown in bold and shaded in each table.

Aquatic toxicity

Tables 12 to 15 contain the acute and chronic aquatic toxicity test results for the active ingredient cyantraniliprole, its metabolites, and the formulated products Benevia and Exirel.

Summary of aquatic toxicity of cyantraniliprole, its metabolites and the formulated products Benevia and Exirel

Acute toxicity

Active

The toxicity of cyantraniliprole exceeded the solubility in the test systems used in the acute studies with fish, with a precipitate or cloudiness apparent in the water. In all cases the LC_{50} values were greater than the solubility of the substance. In the chronic fish studies, the test concentrations were much lower than the water solubility, with the most sensitive species (rainbow trout) 90 day early life stage NOEC 1.01 mg ai/L.

Cyantraniliprole is highly toxic to aquatic invertebrates and a large number of species were tested. The most sensitive crustacean was *Daphnia magna* (48 hour LC_{50} 0.0205 mg/L; 21-day NOEC 0.00656 mg/L).

Metabolites of cyantraniliprole

The toxicity to *Daphnia magnia* of ten metabolites of cyantraniliprole was also tested. The most toxic was IN-PLT97 with 48 hour LC_{50} 0.40 mg metabolite/L. IN-JCZ38 and IN-JSE76 also trigger the HSNO aquatic toxicity thresholds.

Formulations

Benevia was toxic to fish (96 hr LC_{50} 37 mg product/L) and highly toxic to *Daphnia magna* (48 hour EC_{50} 0.0126 mg product/L) and also toxic to green algae (72 hour E_rC_{50} 63.8 mg product/L)

Exirel was highly toxic to *Daphnia magna*, with 48 hour LC_{50} 0.185 mg product/L and also toxic to green algae (72 hour E_rC_{50} 34 mg product/L).

Table 15 Aquatic toxicity – fish (**In bold**: value used for classification and/or risk assessment purposes)

Test species	Test type and duration	Test substance	
		Active	Formulation
		Cyantraniliprole	Benevia
Acute			
Rainbow trout. *Onchorynchus mykiss*	96 hr LC_{50}	>12.6 mg/L (static, mean measured)	
Channel catfish, *Ictalurus punctatus*		>10 mg/L (flow, mean measured)	
Bluegill sunfish, *Lepomis macrochirus*		>13 mg/L(static, renewal, mean measured)	**2.4 mg ai/L (mean measured) tested as 100g/L OD formulation (37 mg product/L)**
Sheepshead minnow, *Cyprinodon variegates*		>12 mg/L (flow, mean measured)	
Chronic			
Rainbow trout. *Onchorynchus mykiss*	90-day ELS flow-through	NOEC 1.01 mg/L LOEC 3.34 mg/L surviving fish length (mean measured)	
Sheepshead minnow, *Cyprinodon variegates*	33-day, ELS, Flow-through	NOEC 2.9 mg/L LOEC 5.8 mg/L fish length (mean measured)	

Table 16 Aquatic toxicity – crustaceans (**In bold**: value used for classification and/or risk assessment purposes)

Test species	Test type and duration	Test substance (mg/L, measured)												
		Active	Metabolites of cyantraniliprole										Formulations	
		Cyantraniliprole	IN-J9Z38	IN-JCZ38	IN-JSE76	IN-K5A77	IN-K5A78	IN-K5A79	IN-XX70	IN-PLT97	IN-QKV54	IN-RNU71	Benevia	Exirel
	Acute													
Daphnia magna	48 hr EC_{50}	**0.0205**	>0.22	1.85	22.46	>0.85	>31.39	>31.57	>0.184	0.40	>0.287	>2.7	**0.00947 mg ai/L (0.126 mg prod/L)**	**0.0185 mg ai/L (0.185 mg prod/L)**
Gammarus pulensis	48 hour LC_{50}	0.172												
Hyallela aztecus		>1.37												
Crayfish, *Procambarus clarkii*		4.0												
Americamysis bahi)	96 hr EC_{50}	1.2												
	Chronic													
Daphnia magna	21-day reproduction	NOEC 0.00656 (length) 0.0147 (no. of	NOEC 0.24 (adult survival)			NOEC 0.117 (length) 1.019 (adult survival)								

Test species	Test type and duration	Test substance (mg/L, measured)												
		Active	Metabolites of cyantraniliprole										Formulations	
		Cyantraniliprole	IN-J9Z38	IN-JCZ38	IN-JSE76	IN-K5A77	IN-K5A78	IN-K5A79	IN-XX70	IN-PLT97	IN-QKV54	IN-RNU71	Benevia	Exirel
		live young)												

Two additional studies on cyantraniliprole were evaluated but considered unreliable for regulatory purposes by the primary OECD reviewer, ie the United Kingdom. These were:

- *Ceriodaphnia dubia* Acute 48hr EC_{50} 0.04 mg cyantraniliprole/L, 7-day reproduction NOEC 0.005 mg cyantraniliprole /L. There was no analytical confirmation of test concentrations and the test did not meet the validity criteria of OECD guideline 211 for numbers of offspring produced.
- *Americamysis bahia* 35-day reproduction NOEC 0.72 mg cyantraniliprole /L. The average number of young per female in the control group was well below the acceptable threshold of three.

One study tested the acute effects of the formulated product Benevia plus Codacide oil on *Daphnia magna*. The 48 hr EC_{50} was 0.018 mg ai/L based on mean measured concentrations. The results were considered reliable with restrictions due the absence of a control group with Codacide alone, the sole control used was the dilution water.

Table 17 Aquatic toxicity – insects, molluscs and other aquatic invertebrates

Test species	Test type and duration	Test substance Cyantraniliprole
Aquatic insects	**Acute**	
Mayfly nymph *Centroptilium triangulifer*	48 hour LC_{50}	0.0715 mg/L (static, mean measured)
Caddisfly larvae, *Lepidostoma Ontario*		0.0748 mg/L (static, mean measured)
Stonefly nymph, *Soyedina carolinensis*		14 mg/L (static, mean measured)
Midge, *Chironomus riparius*	48 hour LC_{50} [water only]	0.719 mg/L (static, mean measured)
Oligochaete, *Lumbriculus variegatus*	48 hour LC_{50}	>13.7 mg/L (static, mean measured)
	Chronic	
Midge, *Chironomus riparius*	28-day, reproduction; spiked water over sediment	EC_{50} 0.010 mg/L (nominal) based on no of adults that did not emerge and mortality of emerged adults NOEC 0.005 mg/L LOEC 0.010 mg/L based on percent emergence
	28-day, reproduction; spiked sediment	NOEC 0.0190 mg/kg sediment LOEC >0.0190 mg/kg sediment
Molluscs	**Acute**	
Eastern oyster, *Crassostrea virginianus*	96 hour EC_{50}	0.45 mg/L (mean measured)

Table 18 Aquatic toxicity –algae and aquatic macrophytes (**In bold**: value used for classification and/or risk assessment purposes)

Test species	Test type and duration	Test substance		
		Active	Formulation	
		Cyantraniliprole	Benevia	Exirel
Algae				
Green alga, *Pseudokirchneriella subcapitata*	72 hour E_rC_{50}	>13 mg/L (mean measured)	**6.62 mg ai/L (mean measured) equivalent to 63.8 mg product/L)**	**3.39 mg ai/L (mean measured) 34 mg product/L**
Anabaena flos-aquae	96 hr E_rC_{50}	>15 mg/L (mean measured) E_bC_{50} 12 mg/L Reliable with restrictions: high variability in control, CV criterion in OECD guideline 201 not met		
Freshwater diatom, *Navicula pelliculosa*	96 hr E_rC_{50}	>14 mg/L (mean measured)		
Marine diatom, *Skeletonema costatum*	72 hour E_bC_{50} 96 hr ErC50	3.2 mg/L (mean measured) >10 mg/L		
Aquatic macrophyte				
Duckweed, *Lemna gibba*	7 day	NOEC 0.0953 mg/L frond necrosis (mean measured) EC_{50} >12.1 mg/L frond count NOEC 1 mg/L		

Aquatic toxicity classifications of cyantraniliprole and the formulated products Benevia and Exirel

Cyantraniliprole is classified as **9.1A highly toxic to the aquatic environment** based on acute toxicity to the crustaceans *Daphnia magna* and *Gammarus pseudolimnaeus* (EC_{50} <1 mg/L). Cyantraniliprole is also highly toxic to a range of other aquatic invertebrates as a result of both acute and chronic exposure, and will be considered further in the aquatic risk assessment.

Formulations

Benevia and Exirel are classified as **9.1A highly toxic to the aquatic environment** based on acute toxicity to the crustaceans *Daphnia magna* (EC_{50} <1 mg/L).

Soil toxicity

Tables 16 to 18 contain the acute and chronic soil toxicity test results for the active ingredient cyantraniliprole and, the metabolites of cyantraniliprole, and the formulated products Benevia and Exirel.

Summary of toxicity of Cyantraniliprole, its metabolites and the formulated products Benevia and Exirel to soil organisms

Earthworms and other soil macro-invertebrates

Cyantraniliprole, its metabolites and the product Benevia did not exhibit toxicity to earthworms as a result of either acute or chronic exposure, with LC_{50} values >1000 mg/kg soil.

The collembolan *Folsomia candida* is more sensitive that the earthworm, with reproduction LOEC 0.12 mg ai/kg soil. The IN-JCZ38 and IN-RNU71 metabolites also affected reproduction at 12 and 12.5 mg metabolite/kg soil respectively under laboratory conditions. In a field study examining overall changes in collembolan populations, there were transient changes on the abundance of different taxa, but the class as a whole was not affected.

The soil mite *Hypoapsis aculeifer,* had a similar sensitivity to that of the earthworm, with 14-day reproductive NOEC of 100 mg/kg soil for cyantraniliprole and most metabolites, with the exception of IN-QKV54 and IN-RNU71 where the NOEC was 100 mg metabolite/kg soil.

In a litter bag study to determine the effects of cyantraniliprole on population density and species distribution of micro-arthropods, there were no statistically significant differences between the treated and control plots.

Soil micro-organisms

There were no significant effects on soil microbial function at rates up to ten times the standard application rate.

Terrestrial plants

There were some deficiencies in the studies on terrestrial plants, however, it can be concluded that Benevia had no significant effects on seedling emergence or vegetative vigour, neither after pre-emergence,

application to soil surface nor after post-emergence foliar application (21-day ER50> 150 g a.i./ha for all species). This application rate is higher than that proposed for New Zealand use.

Table 19 Soil toxicity – earthworm, soil arthropods

Test species	Test type, duration, endpoint	Test substance (mg/kg soil, nominal)										
		Active		Metabolites of cyantraniliprole								Formulation
		Cyantraniliprole	IN-J9738	IN-JCZ38	IN-JSE76	IN-K5A77	IN-K5A78	IN-KA79	IN-PLT97	IN-QKV54	IN-RNU71	Benevia
Earthworm, *Eisenia fetida*	Acute, 14-day LC_{50}	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000	-	-	>1000 mg product/kg
	Reproduction, 56-day, NOEC	1000	1029	1059	1000	1000	1036	1185	1000	100	100	>1000 mg product/kg
Springtail, *Folsomia candida*	Reproduction 28-day, NOEC mortality and reproduction	0.08 adult mortality LOEC 0.12	500 adult mortality; 1000 repro	12	250	<62.5	1000	125	1000	98.3	12.5	
Soil mite, *Hypoaspis aculeifer*	Reproduction, 14-day, NOEC mortality and reproduction	1000	1000	1000	1000	1000	1000	1000	500	100	100	

Table 20 Soil toxicity – terrestrial plants

Test species	Test type and duration	Test substance	
		Benevia	**Benevia + Codacide oil spray adjuvant (95% rapeseed oil)**
Six dicot and four monocot crop species Tomato, sugarbeet, soybean, pea, oilseed rape, cucumber, perennial ryegrass, onion, oat, corn	Vegetative vigour, 21 days Foliar application to seedling plants	ER_{25} and ER_{50} >1.43 L product/ha (equiv to >150 g ai/ha) (Tier I) **Study rated as unreliable for onion, cucumber, ryegrass, sugarbeet and tomato due to phytoxicity in control plants, and other deviations from the test protocol** **Reliable for corn, oat, ryegrass, oilseed rape, soybean, pea**	ER_{50} >1.5 L product/ha (equiv to >150 g ai/ha) all species (Tier I) NOER 75 g ai/ha onion for shoot dry weight (Tier II) **Fully reliable, variations in environmental conditions had no significant effect on test results**
	Seedling emergence, 21 days Application to soil surface	ER_{50} >1.43 L product/ha for all species (equiv to >150 g ai/ha) (Tier I) **Study rated as unreliable and not suitable for regulatory risk assessment** **Several significant deviations from OECD 208 test protocol, (including phytotoxicity in control plants)**	NOEL 1.5 L product/ha (150 g ai/ha) for onion ryegrass, pea (Tier II) NOEL 0.38 L product/ha (37.5 g ai/ha) for tomato based on effects on shoot weight (Tier II) **Study rated as unreliable for oat, onion, ryegrass, pea and tomato limit tests due to phytoxicity in control plants, and other deviations from the test protocol** **Reliable for corn, cucumber, oilseed rape, soybean and sugarbeet limit test (Tier I) and ryegrass and tomato rate response test (Tier II)**

Table 21 Soil toxicity – soil microbial function

Test species	Test type and duration	Test substance (mg/kg soil, nominal)										
		Active	Metabolites of cyantraniliprole									Formulation
		Cyantraniliprole	IN-J9738	IN-JCZ38	IN-JSE76	IN-K5A77	IN-K5A78	IN-KA79	IN-PLT97	IN-QKV54	IN-RNUJ71	Benevia
Soil microbial function												
Soil microflora	Nitrogen mineralisation, 28 days,	<25% effect 1.41 [10 x max rate]	<25% effect 1.38	<25% effect 1.45	<25% effect 1.48	<25% effect 1.40	<25% effect 1.41	<25% effect 1.69	<25% effect 1.49	<25% effect 2.03	<25% effect 2.16	<25% effect 1.24 mg ai/kg soil (12.4 mg product/kg)
	Carbon mineralisation, 28 days											
Soil micro-organisms	Degradation of litter under field conditions, 6 months	-	No sig effects	Not tested	No sig effects	No sig effects	No sig effects	No sig effects	No sig effects	Not tested	Not tested	No significant effects in straw decomposition, substance applied to soil at plateau concentration

Field studies for toxicity to the soil environment

Collembola population density and species distribution

A GLP study was conducted to determine potential effects of cyantraniliprole on the population density and species distribution of Collembola (springtails) under field conditions near Bodelshausen, Baden-Württemberg, Southern Germany. For this purpose community composition and abundance of selected soil living invertebrates were monitored over the period of six months. The test consisted of 6 treatments – control, 4 test item treatment groups and a toxic reference treatment. The soil at the field site was classified as a silty clay (DIN 4220) with a pH of 7.05 and a total organic carbon content of 4.5 %. The individual test plots had a size of 4 m x 6 m with 6 replicates per treatment. Two applications were performed on short cutted grass, the first application was done on 10 June 2010 and the second application took place 7 days later (17 June 2010). At the first application cyantraniliprole was applied at 17.9 g a.i./ha, 142.2 g a.i./ha, 293.6 g a.i./ha and 1502.2 g a.i./ha for the test item treatments T1 (100g/L OD), T2 (100g/L OD + Codacide Oil), T3 (100g/L SE + Codacide Oil), T4 (200g/L SC), respectively. The actual mean amounts applied at the second application were 13.2 g a.i./ha, 100.8 g a.i./ha, 201.8 g a.i./ha and 958.8 g a.i./ha for test item treatments T1,T2, T3, and T4 respectively. At both applications the control plots were treated with tap water. Soil core samplings for microarthropod extraction were conducted 10 days before the second application, 27 days after the second application, 88 days after the second application, 159 days after the second application and 368 days after the second application. In total 12,018 Collembola were collected during 5 sampling occasions, 1,931 of them in the control plots, corresponding to approximately 8,195 ind./m². Eleven Collembola families with 26 species could be identified.

Based on the results of this Collembola field study it can be concluded that the application of cyantraniliprole applied twice with different formulations 100g/L (OD) with and without Codacide Oil, 100g/L (SE) with Codacide Oil and 200g/L (SC)) at up to 1400 g plus 1000 g Cyantraniliprole/ha had some transient effects on individual taxa. The class Collembola as a whole was not affected by any of the cyantraniliprole treatments.

There were reductions in the second sampling (27 days after the second application) and third sampling (88 days after the second application) for individual taxa in T2 and T4 treatments. By the fourth (159 days after second application) and fifth last sampling (368 days after the second application) there were no significant reductions but there was a significant increase for total undetermined Entomobryidae with treatment T3 (280 g plus 200 g/ha including 5 L Codacide Oil/ha each time) and for *Isotomiella minor* with treatment T1 (17.5 g plus 12.5 g Cyantraniliprole/ha), respectively.

The study was classified as reliable with restrictions due to some deviations from the trial.

Soil micro-arthropods – litter bag study

A GLP monitoring study to determine the effects of cyantraniliprole on the population density and species distribution of soil microarthropod fauna was conducted according to the ISO 23611-2. The study took place on plots of a litter bag study (S09-01163) treated with cyantraniliprole near Oberacker, Baden-Wuerttemberg/Germany on an arable site cultivated with summer wheat and white clover. The first application of cyantraniliprole was applied to bare soil at 53 g ai/ha and incorporated into the soil to a depth

of 10 cm. Wheat was sown on the ground direct before the tillage operation. A second application of 300 g cyantraniliprole/ha was applied 11 days after the first application. The control plots were treated with tap water. Soil core sampling for microarthropod extraction was conducted 143 days after the second application. In total 798 Collembola and 2258 Acari were collected corresponding to approximately 7000 Collembola/m² and 19000 Acari/m². For the Collembola 12 species could be identified, for the mite family Oribatidae 5 species. No statistically significant differences between the test item treatment and the control were found for any taxon analyzed.

In addition a non-GLP soil microarthropod sampling was carried out on the same plots 92 days after the second application. Fewer specimens were caught during this sampling occasion (in total 373 Collembola and 1445 Acari). Differences between the test item treatment and the control plots were not statistically significant.

The study is classified as reliable with restrictions for regulatory purpose because no toxic reference substance was applied to control plots to evaluate the sensitivity of the system to toxic substances.

Classification of cyantraniliprole, Benevia and Exirel for toxicity to the soil environment

Cyantraniliprole, the metabolites of cyantraniliprole and the two formulated products, Benevia and Exirel do not trigger the HSNO thresholds for toxicity to the soil environment.

Terrestrial vertebrate toxicity

For effects on terrestrial vertebrates other than birds, refer to the mammalian toxicity section.

Table 19 contains the acute and chronic avian toxicity test results for the active ingredients cyantraniliprole, its metabolites, and the formulated product Benevia. No test data were provided for the toxicity of Exirel to birds.

Summary of toxicity of cyantraniliprole, Benevia and Exirel to birds

Acute and short-term dietary toxicity

Cyantraniliprole was not toxic to birds as a result of either an acute oral dose or short-term dietary exposure. No signs of toxicity or mortality occurred in any of the studies.

Sub-chronic and reproduction toxicity

There were no effects on any reproductive parameters or adult birds in either the bobwhite quail or mallard reproductive studies. In both cases, the NOEC was the highest dietary concentration tested.

Table 22 Terrestrial vertebrate toxicity

Test species	Test type, duration, endpoint	Test substance	
		Cyantraniliprole	Benevia
Bobwhite quail, *Colinus virginianus*	Acute oral LD_{50}	>2250 mg/kg bw	>2250 mg/kg bw
	5-day dietary LC_{50}	>5620 ppm diet (>1343 mg/kg bw/day)	
	Reproductive 1 generation, 22 weeks	NOEC 1000 ppm diet (93.2 mg/kg bw/day) [highest dose]	
Mallard duck, *Anas platyrynchos*	5-day dietary LC_{50}	>5620 ppm diet (>2583 mg/kg bw/day)	
	Reproductive 1 generation, 21 weeks	NOEC 1000 ppm diet (139.6 mg/kg bw/day) [highest dose]	
Zebra finch, *Taeniopygia guttata*	Acute oral LD_{50}	>2250 mg/kg bw	

Classification of cyantraniliprole, Benevia and Exirel for toxicity to terrestrial vertebrates

Neither cyantraniliprole nor the two formulations trigger the HSNO thresholds for toxicity to terrestrial vertebrates based on the data available.

Ecotoxicity to terrestrial invertebrates

Tables 20 to 24 contain the acute and chronic toxicity test results for the active ingredient cyantraniliprole and the formulated products Benevia and Exirel.

Summary of toxicity of cyantraniliprole, its metabolites and the formulated products to terrestrial invertebrates

Honey bees

Active - cyantraniliprole

Definitive acute LD_{50} values cyantraniliprole were not determined, with the highest dose tested being insufficient to be conclusive. The acute oral and contact toxicity of cyantraniliprole were 48 hour oral LD_{50} >0.1055 μg/bee and 72 hour contact LD_{50} >0.0934 μg/bee. In the oral study, bees were observed to be 'apathetic' after 24 hours, but normal after 48 hours. At the highest treatment rate, consumption of solution was markedly reduced relative to controls, suggesting possible avoidance of the substance or repellency. In the contact study, there was 34% mortality at the highest dose and some abnormal behaviour at all doses, with bees categorised as 'apathetic' or 'moribund'.

Metabolites of cyantraniliprole

IN-HGW87(a plant metabolite) was highly toxic via oral exposure (72 hour LD_{50} 0.298 μg/bee), with 97.9% mortality at the highest dose tested 1.8 μg/bee after 48 hours. Abnormal behaviour was observed at all dose levels after 48 hours.

IN-J9Z38 and IN-K5A78 both had oral LD_{50} values higher than the single dose tested (>8.34 ng/bee and >45.61 μg/bee respectively). In the study with IN-J9Z38 there was 8% mortality and some abnormal behaviour in the first four hours after treatment. No further study was performed with metabolites.

Formulations

Benevia

Benevia was acutely toxic to bees with 72 hour oral LD_{50} 3.79 μg product/bee (0.39 μg ai/bee; NOEL 0.835 μg product/bee). At four hours the majority of bees were 'apathetic' at all test concentrations, and survivors still apathetic at 24 hours.

In the acute contact study, the 96 hour LD_{50} was 6.31 μg product/bee (0.65 μg ai/bee). The test was extended to 96 hours due to increasing mortality (>10%) between 24 and 48 hours. Abnormal behaviour occurred at all test concentrations at 24 and 48 hours. At 96 hours surviving bees appeared normal

A series of semi-field studies were undertaken with the formulated product.

Exirel

The acute oral study with Exirel was extended to 96 hours due to increasing mortality (>10%) between 24 and 48 hours. The LD_{50} was 8.76 μg product/bee (0.92 μg ai/bee) and a NOEL could not be determined. Abnormal behaviour occurred at all test concentrations at 24 and 48 hours. At 96 hours surviving bees appeared normal.

The acute contact study was also extended to 96 hours for the same reasons, with 96 hour LD_{50} 26.47 μg product/bee (2.78 μg ai/bee). Abnormal behaviour was observed at all dose levels up to 72 hours. At 96 hours surviving bees appeared normal.

Other non-target arthropods

The predatory mite, *Typhlodromus pyri* was not adversely affected in laboratory studies with Benevia and Exirel. The LR_{50} for Benevia was >2300 mL product/ha and for Exirel > 3000 mL product/ha.

In field studies assessing natural predatory mite populations in European vineyards, there were no statistically significant effects on those populations relative to controls.

Parasitic wasp, *Aphidius rhopalosiphi*

The parasitic wasp, *Aphidius rhopalosiphi* is more sensitive to cyantraniliprole, with 48 hour LR_{50} 1.019 mL Benevia/ha and 0.95 mL Exirel/ha under standard laboratory conditions. Exposure to dry residues on barley resulted in 48 hour LR_{50} 8.22 mL Benevia/ha (Exirel not tested).

Further extended laboratory studies included the addition of the spray additive Codacide oil (95% rapeseed oil), and while it is not possible to separate the effects of the additive from that of the formulation, there was significant mortality as a result of exposure to freshly dried residues of Benevia, with reproduction reduced by 40.5% following exposure to 27 day-old residues. No repellent effects were observed in the study.

In the extended laboratory study with Exirel plus Codacide oil, the 48hour LR_{50} could not be determined, with ER_{50} for reproductive effects <22 mL Exirel/ha, the lowest rate tested.

Direct over-spray of mummies resulted in a rate-related decrease in reproduction, 38.5% at 1500 mL Benevia/ha.

Under semi-field conditions with exposure to freshly dried residues, there were statistically significant reductions in reproduction ranging from 59.9 – 99.5% when tested at 60, 120 and 180 ml Benevia/ha (+codacide oil). When tested in a second study at 22 mL Benevia/ha (+ 36.7 mL codacide oil), parasitism rates were not affected relative to controls.

Exirel also adversely affected parasitism rates under semi-field conditions. When tested at 30, 60, 90, 120 and 180 mL Exirel/ha (+codacide oil), effects on parasitism varied from 90.7 – 100%).

Ladybird *Coccinella semptempunctata*

The 19-day LR_{50} for ladybird *Coccinella semptempunctata* was 615 mL Benevia/ha and 433 mL Exirel/ha when exposed to fresh residues on bean leaves in an extended laboratory study. There were no effects on reproduction up to 600 mL Benevia/ha and 250 mL Exirel/ha.

Under extended laboratory conditions with exposure to aged residues of Benevia (+codacide oil), there was 66.7% morality two days after the second application and <50% effect on reproduction relative to controls at 14 days and 28 days after the second application.

Green lacewing *Chrysoperla carnea*

Under extended laboratory conditions, the 19-day LR50 was 2609 mL Benevia/ha and 2126 mL Exirel/ha. For Benevia, there were no adverse effects on reproduction up to and including 1260 mL product/ha, the highest rate not substantially affected by morality. For Exirel, there were no adverse effects on reproduction up to and including 1731 mL product/ha, the highest rate not substantially affected by mortality.

Table 23 Terrestrial invertebrate toxicity – honey bees *Apis mellifera*, Tier 1 laboratory studies (**In bold**: value used for classification and/or risk assessment purposes).

Test type, duration. endpoint	**Test substance**					
	Active	**Metabolites**			**Formulations**	
	Cyantraniliprole	IN-HGW87	IN-J9Z38	IN-K5A78	Benevia	**Exirel**
Acute oral, 48 hr LD_{50}	>0.1055 μg/bee (actual measured intake) 12% of bees at highest dose classified as "apathetic" after 24 hours, no abnormal behaviour at 48 hours At lowest treatment rate (0.0292 μg/bee) bees consumed a similar amount of solution to the control bees. At the highest treatment rate (0.1055 μg/bee) bees consumed 45% less solution than control bees		>8.34 ng metab/bee (limit test, measured intake) 8% mortality, one bee observed to be 'cramping' after 4 hours, no abnormal behaviour at 24 and 48 hours	>45.61 μg metab/bee (actual measured intake) NOEL 45.61 μg metab/bee		
Acute oral, 72 hr LD_{50}		0.298 μg metab/bee (actual measured intake) NOEL 0.143 μg metab/bee Maximum mortality of 97.9% mortality at highest dose (1.8 μg metab/bee) after			**3.79 μg product/bee (0.39 μg ai/bee) measured intake NOEL 0.835 μg product/bee (0.086 μg ai/bee)** At 4hr, the majority of bees at all test concentrations were	

Test type, duration. endpoint	Test substance					
	Active	Metabolites			Formulations	
	Cyantraniliprole	IN-HGW87	IN-J9Z38	IN-K5A78	Benevia	**Exirel**
		48 hours. Abnormal behaviour at all dose levels after 48 hours. Mortality increased by more than 10% between the 24 and 48 hour observations but the test was not extended to 96 hours.			classed as apathetic. At 24 hr, surviving bees were still apathetic at the two highest doses (1.4 and 3 μg ai/bee)	
Acute oral, 96 hr LD_{50}						**8.76 μg product/bee (0.92 μg ai/bee) measured intake** **NOEL could not be determined** The test was extended to 96 hours due to mortality increasing by more than 10% between the 24 and 48 hour observations. Mortality reached a maximum of 92% at the highest dose (19.2 μg ai/bee) after 96 hours. Abnormal behaviour was observed in bees at all

Test type, duration. endpoint	Test substance					
	Active	Metabolites			Formulations	
	Cyantraniliprole	IN-HGW87	IN-J9Z38	IN-K5A78	Benevia	**Exirel**
						Test concentrations at 24 and 48 hours. At 96 hours, no abnormal behaviour was observed in surviving bees All treatment groups consumed less than controls, no direct correlation between test concentration and amount consumed
Acute contact, 48 hr LD_{50}	>0.0934 μg/bee (nominal)				**11.64 μg product/bee** (nominal) 1.2 μg ai/bee (nominal) no abnormal behaviour was observed in surviving bees	**28.8 μg product/bee** (nominal) 3.03 μg ai/bee (nominal) no abnormal behaviour was observed in surviving bees
Acute contact, 72 hr LD_{50}	>0.0934 μg/bee (nominal) 34% mortality at the highest dose (0.0934 μg/bee). Some abnormal behaviour at all dose levels – bees were categorised as 'apathetic' or 'moribund'					

Test type, duration. endpoint	Test substance					
	Active	Metabolites			Formulations	
	Cyantraniliprole	IN-HGW87	IN-J9Z38	IN-K5A78	Benevia	Exirel
Acute contact, 96 hr LD_{50}					6.31 μg product/bee (0.65 μg ai/bee) nominal NOEL 1.84 μg product/bee (0.19 μg ai/bee) nominal The test was extended to 96 hours due to mortality increasing by more than 10% between the 24 and 48 hour observations. Mortality reached a maximum of 80% at the highest dose (2.0 μg ai/bee) after 96 hours At 4hr, the majority of bees at all test concentrations were classed as apathetic. At 24 hr, surviving bees were still apathetic at the two highest doses (1.4 and 3 μg ai/bee). At 96 hours, no abnormal behaviour	26.47 μg product/bee (2.78 μg ai/bee) nominal NOEL could not be determined The test was extended to 96 hours due to mortality increasing by more than 10% between the 24 and 48 hour observations. Mortality reached a maximum of 94% at the highest dose (16 μg ai/bee) after 96 hours Abnormal behaviour was observed at all dose levels up to 72 hours. At 96 hours, no abnormal behaviour was observed in surviving bees

Test type, duration. endpoint	Test substance					
	Active	Metabolites			Formulations	
	Cyantraniliprole	IN-HGW87	IN-J9Z38	IN-K5A78	Benevia	**Exirel**
					was observed in surviving bees	

Table 24 Terrestrial invertebrate toxicity –honey bees, extended laboratory and semi-field studies

Test species	Test type, duration. endpoint	Test substance Benevia (100 g/L OD)
Honeybee, *Apis mellifera*	Extended lab test, 24 hour exposure to dried residues on alfalfa	Plants treated at 1.5 L product/ha. Residues aged for 3, 8, 24, 48 and 72 hours prior to exposure Mortality <25% at all concentrations tested. Small numbers of bees exhibited abnormal behaviour but not in a dose-related pattern

Test species	Test type, duration. endpoint	Test substance Benevia (100 g/L OD)
Apis mellifera mellifera	Semi-field (140 m^2 tunnel), wheat treated with artificial honeydew France 2008	Wheat treated with sugar solution to simulate honeydew. Benevia applied at 10 g ai/ha and 100 g ai/ha before bee flight and during bee flight. Water and dimethoate controls At 100 g ai/ha and 10 g ai/ha applied during flight, there was limited short-term effect on mortality (increased for 3 days after application (DAA)) and an effect on foraging behaviour, with foraging activity decreased 4 – 6 DAA). The cyantraniliprole formulation may be repellent to bees under the conditions of the test When applied before flight, there was no effect on mortality, and there was an effect of foraging similar to that in higher application rate treatment When applied after flight, there was a minor and temporary increase in mortality and an effect on foraging **Study rated as reliable with restrictions**. The UK reviewer could not obtain the test protocol used and therefore evaluated the study according to EPPO 170 and OECD 75. The study was GLP compliant Only one replicate was used for the test item and each treatment group. Two of the treatment groups were applied after bee flight, whereas the toxic reference and control were applied during bee flight, therefore the results from application during flight are considered more reliable. Colony strength and brood development assessments were only carried out until DAA+6, which is not long enough to derive endpoints regarding these parameters
Apis mellifera mellifera	Semi-field (140 m^2 tunnel), treated phacelia *Phacelia tanacetifolia* France 2008	Benevia applied at 10 g ai/ha and 100 g ai/ha before bee flight and during bee flight. Water and dimethoate controls At 100 g ai/ha and 10 g ai/ha applied during flight and at 100 g ai/ha before flight, there was an effect on mortality and on foraging behaviour, with foraging activity decreased). At 10 g ai/ha after flight there was an effect on foraging behaviour only The cyantraniliprole formulation may be repellent to bees under the conditions of the test **Study rated as reliable with restrictions**. [for the same reasons indicated for the study on treated wheat]

Test species	Test type, duration. endpoint	Test substance Benevia (100 g/L OD)
Apis mellifera carnica	Semi-field (140 m^2 tunnel), treated phacelia *Phacelia tanacetifolia* Germany 2008	Two different test item treatment groups (T1 and T2) with Cyantraniliprole 100 g/L OD applied at different rates in separated tunnel tents, another group treated with the reference item I (dimethoate), and a control group where tap water was applied. In each replicate of the two test item treatment groups, Cyantraniliprole 100 g/L OD was applied twice; once before flowering (BBCH 55–57 before hive set-up) and once 14 days later during full flowering and bee-flight (BBCH 65). In the treatment group T1, each application was carried out at a rate of 10 g cyantraniliprole/ha. In the treatment group T2, each application was carried out at a rate of 100 g cyantraniliprole/ha. At application rates of 100 g ai/ha, honey bee mortality increased on the day of the second application (during full flowering and bee-flight) and on the next day. At application rates of 10 g ai/ha, there was no increase in honey bee mortality Cyantraniliprole 100 g/L OD, applied during full flowering and bee-flight at rates of 10 g or 100 g ai/ha, had an effect on honey bee flight activity. At 10 g ai/ha, there was a significant reduction of honey bee flight activity on the day of the application. At 100 g ai/ha, flight activity in the crop was significantly reduced on the day of the application and on the next day It can be concluded that the test item Cyantraniliprole 100 g/L OD, applied twice (once before flowering and set-up of the bee colonies, and 14 days later during full flowering and bee-flight), with each application at rates of 10 g ai/ha (treatment group T1) or with each application at rates of 100 g ai/ha (treatment group T2), showed no obvious test item related impact on the honey bee brood development Both treatments resulted in temporary intoxication symptoms being observed **Study rated as fully reliable**
Apis mellifera carnica	Semi-field (108 m^2 tunnel), treated phacelia *Phacelia tanacetifolia* with additional assessment of effects on colony and brood development	Cyantraniliprole 100 g/L OD plus Codacide oil was sprayed twice at a rate of 150 g ai./ha (equivalent to 2 × 1500 mL Cyantraniliprole 100 g/L OD formulated product) + 2.5 L Codacide oil/ha, respectively, with an application interval of 15 days. During the first and second applications, the *Phacelia tanacetifolia* was in growth stage BBCH 58 and BBCH 65, respectively. The 1^{st} spray application was performed onto the non-flowering Phacelia crop whilst the second application was performed during full flowering in the evening after daily bee flight

Test species	Test type, duration. endpoint	Test substance Benevia (100 g/L OD)
		Following the 2nd application there was a distinct but short-term effect on honey bee mortality and foraging activity due to Cyantraniliprole 100 g/L OD plus Codacide oil. No effects on colony development or colony strength were observed. With respect to the bee brood development, Cyantraniliprole 100 g/L OD plus Codacide oil caused no effects on the brood nest size (brood stages in cm^2/colony), survival of marked eggs (brood termination rate), brood development from eggs into adult bees (brood index), and brood compensation ability (brood compensation index) The test item treatment resulted in temporarily increased mortality and temporarily increased flight activity. Some symptoms of intoxication were observed, but not on a large scale and these did not persist. There was no treatment related effect on the colony strength or brood development observed **Study rated as fully reliable**

Table 25 Terrestrial invertebrate toxicity – honey bees, field studies with Benevia

Study type/ crop/species	Rate(s) tested and timing	Mortality	Flight activity and Behavioural effects	Impact on colonies	Reference
Field/ *Brassica napus/ Apis mellifera carnica*	1.5 L form/ha (150 g a.s./ha) plus 2.5 L codacide oil applied once before flowering and once during flowering after bee flight 1.5 L form/ha (150 g a.s./ha) plus 2.5 L codacide oil applied once before flowering and once during flowering during bee flight	No impact on mortality as a result of the first application. Second applications after and during bee flight slightly increased mortality	No impact on flight activity or behaviour as a result of the first applications. Second applications after bee flight slightly reduced flight activity on the day following application. Second application during bee flight did not impact on flight activity. Some behavioural effects were seen after the second applications	No effect on colony strength or brood development	DuPont-27323[a]
Field/ *Brassica napus/ Apis mellifera carnica*	1.5 L form/ha (150 g a.s./ha) plus 2.5 L codacide oil applied once before flowering and once during flowering after bee flight 0.125 L form/ha (12.5 g a.s./ha) plus 2.5 L codacide oil applied once before flowering and once during flowering during bee flight	No impact on mortality as a result of the first applications Second application of 150 g a.s./ha slightly increased mortality	No impact on flight activity or behaviour as a result of the first applications Second applications slightly reduced flight activity. Some behavioural effects were seen after the second applications	No effect on colony strength or brood development	DuPont-27324 Reliable with restrictions
Field/ *Brassica napus/ Apis mellifera carnica*	1.5 L form/ha (150 g a.s./ha) plus 2.5 L codacide oil applied once before flowering and once during flowering after bee flight	No impact on mortality after either application	Slight impact on flight activity after second application of 12.5 g a.s./ha. Flight activity was too consistently low in 150 g a.s./ha group to identify if an	No effect on colony strength or brood development	DuPont-27326 Reliable with restrictions

	0.125 L form/ha (12.5 g a.s./ha) plus 2.5 L codacide oil applied once before flowering and once during flowering during bee flight		effect on flight activity had occurred. No effect on behaviour resulted from the first applications or second application of 12.5 g a.s./ha. The second application of 150 g a.s./ha had an effect on behaviour		
Field/ Brassica napus/ Apis mellifera carnica	90 g a.s./ha plus 2.5 L codacide oil applied once before flowering and once during flowering after bee flight 90 g a.s./ha plus 2.5 L codacide oil applied once before flowering and once during flowering during bee flight	No impact on mortality due to first applications or second application after bee flight. Impact on mortality due to second application during bee flight	No impact on behaviour after first applications or second application after bee flight. Slight effect on behaviour after second application during bee flight. No impact on flight activity after first applications. Flight activity reduced for a few days after second applications Flight activity in the control was <3 bees/m2 on the days of second application in the treatment groups. The low flight activity seen in the control group at the time of the second application s of T1 and T2 meant that the results from the test groups could only be compared to these low levels. This could have meant that the test item related effects on flight activity were not as	No effect on colony strength or brood development	DuPont-29571 Reliable with restrictions

			pronounced as they could have been		
Field/ *Brassica napus/ Apis mellifera carnica*	90 g a.s./ha applied once before flowering and once during flowering after bee flight. T1 90 g a.s./ha applied once before flowering and once during flowering during bee flight. T2	No impact on mortality due to first applications or second application after bee flight. T1 Effect on mortality due to second application during bee flight.T2 lasting until 5 days after treatment	No impact on flight activity due to first applications or second application after bee flight.T1 No impact on or behaviour due to first applications. Slight impact on behaviour due to second application after bee flight. Slight impact on flight activity and behaviour due to second application during bee flight	No effect on brood development due to applications after bee flight. No effect on colony strength due to applications after bee flight. Possible effect on overwintering capacity of colonies due to applications during bee flight (T2), shown by lower mean colony strength after overwintering compared to control	DuPont-29572 Reliable with restrictions
Field/ Melon/ *Apis mellifera*	90 g a.s./ha plus 2.5 L codacide oil applied once at the beginning of flowering and once during full flowering after bee flight T1 90 g a.s./ha plus 2.5 L codacide oil applied once at the beginning of flowering and once during full flowering during bee flight T2	No impact on mortality after first or second applications after bee flight. T1 Slight impact on mortality after first application during bee flight. T2 No impact on mortality after second application during bee flight. T2	No apparent effect on flight activity after first or second applications after bee flight.T1 Possible effect on flight activity after first application during bee flight T2, by comparison to pre-application levels, but not compared to the control. No apparent effect on flight activity after second application during flowering.	No effect on colony strength or brood development indicated in interim report; results of final report need to be considered when information on colony strength and brood development after overwintering are available. (Due later in 2012)	DuPont-31672 interim report only, reliable with restrictions

			Noted that control flight activity was very low. No behavioural effects seen after applications after bee flight. T1 First application during bee flight had impact on behaviour, whereas second application during bee flight had no impact. T2		

Table 26 Terrestrial invertebrate toxicity – Bumble bees, extended laboratory and semi-field studies

Test species	**Test type, duration. endpoint**	**Test substance**	
		Formulations	
		Benevia	**200 g/L SC (included as additional information only, not a formulation considered in this application)**
Bumble bees, *Bombus terrestris*	Semi-field (greenhouse), on tomato crop	Benevia + Codacide oil At 10 g ai/ha + 0.25%v/v by spray application 15, 8 and 2 days before release of bumble bees (T3) and 14, 7 and 1 day prior to release (T4). – no adverse effects on mortality, foraging, and development of brood relative to water controls A potentially treatment related effect on queen mortality was observed	At 100 g ai/ha applied by drip irrigation 21, 14 and 7 days before release of bumble bees in one compartment (T1), and 14, 7 and 1 day in a second compartment (T2) – no adverse effects on mortality, foraging, and development of brood relative to water controls A potentially treatment related effect on queen mortality was observed
		Study rated as reliable with restrictions – conducted to GLP but no standard test method available so assessed on its own merit by UK reviewer. No reference substance was used so it was unclear if the exposure methods were suitable. Unclear how foraging activity was assessed. In treatment group T3, the last spray application was 14.62% less than the target rate and the results not adjusted, the conclusions drawn for this treatment is an overestimate ie the endpoint is too high. No control was used in the drip irrigation trial. All applications were made before hives were moved into the greenhouses; therefore exposure was to residues only, not direct overspray. No settling in	

Test species	Test type, duration. endpoint	Test substance	
		Formulations	
		Benevia	200 g/L SC (included as additional information only, not a formulation considered in this application)
		period prior to exposure which is not consistent with recommendations in EPPO 170. The experimental phase was from November to December which may not be an ideal time for studying effects on the bumblebee	

Semi-field/field tests including Codacide oil

A further twenty three further semi-field or field studies conducted to GLP were undertaken to assess the effects of cyantraniliprole formulations plus Codacide oil on honeybees on a range of crops under European conditions. None of those studies indicated any adverse impact on honey bee mortality, flight intensity, behaviour or brood development not already indicated in studies with the formulations without the addition of Codacide oil.

Additional bee studies – supporting information only, not fully reliable

Comparative toxicity of Benevia and Exirel in combination with the spray additive Codacide spray oil

Laboratory

A series of non-GLP tests were undertaken to assess the relative oral and contact toxicity of Benevia and Exirel in combination with the spray additive Codacide oil and Codacide oil alone. The full study was not supplied and the summary lacked sufficient information for a full evaluation, but can be used as part of a weight-of-evidence approach. NOTE – the draft New Zealand labels for Benevia and Exirel do not mention the addition of Codacide oil when applying these products but refer instead to “a non-ionic surfactant”. However, the summary information is included here for completeness, and may be of relevance in future if approval is sought for other formulations.

The application (contact test) or feeding (oral test) of the additive codacide oil did not cause any effect on the honey bees at the tested concentration rates. The food uptake in the oral treatment was comparable to the control group and therefore no repellent effect of codacide oil was observed.

No differences in mortality were observed between the oral toxicity test with Cyantraniliprole 100 g/L SE (Exirel) and the contact toxicity test with Cyantraniliprole 100 g/L OD (Benevia) with or without codacide oil.

There was no mortality in the oral toxicity test with Cyantraniliprole 100 g/L OD (Benevia). In the oral toxicity test with Cyantraniliprole 100 g/L OD + 0.25% codacide oil there was higher mortality and a reduced food uptake.

The contact toxicity test with Cyantraniliprole 100 g/L SE (Exirel) combined with codacide oil at 0.28 μg ai/bee had mortality that was two times greater compared to the same dose level of Cyantraniliprole 100 g/L SE without codacide oil. Mortality was comparable between treatments at both higher dose levels (0.93 and 2.8 μg ai/bee).

In the oral treatment with Cyantraniliprole 100 g/L OD (Benevia) some affected bees were observed (reduced coordination) at the assessment 4 hours after start of feeding, but these bees totally recovered by the next assessment (24 hours). In all other Cyantraniliprole 100 g/L OD and Cyantraniliprole 100 g/L SE treatments, sub-lethal effects (reduced co-ordination, apathetic, moribund and cramping bees) were observed 4, 24, and in some cases up to 48 hours after treatment. Recovery was observed in surviving bees by the end of the test period. No sub-lethal effects were observed in any test item treatment 72 hours after treatment.

Residues in nectar and pollen

The following data on the translocation of cyantraniliprole is included for completeness, no evaluation of effects on bees were undertaken in these studies, only the translocation of the substance and identification of metabolites measured.

Table 27 Summary of the translocation of [^{14}C]-cyantraniliprole into pollen and stamens*

Test item	Study type/species	%TRR, mg/kg		Main metabolites	Reference
		Foliar application	Soil application		
^{14}C - Cyantraniliprole	Translocation into pollen and stamens/ canola, sunflower, tomato, zucchini	34.7-75.6%	49.3-64.7%	IN-J9Z38 IN-MLA84 IN-HGW87	DuPont-17705, Revision No. 1
^{14}C - Cyantraniliprole	Translocation into pollen and stamens/ *Phacelia tanacetifolia*	17.3%	29.0-54.4%	IN-DBC80 IN-J9Z38 IN-JCZ38 IN-K5A77 IN-K5A78	DuPont-26578

Field residues measured in pollen and nectar (no evaluation undertaken of effects on bees) where the 100 g/L OD formulation is Benevia and the 100g/L SE formulation is Exirel , all values are expressed as μg/kg.

Table 28 Summary of honey bee field trials to evaluate maximum residues detected in nectar and pollen from experimental crops

Residue values in bold and underlined represent maximum values. * Means residues <LOQ of 5.0 μg/kg. na Not applicable

Test substance	Crop	Rate g ai/ha	Use type	Matrix	Cyantraniliprole	IN-J9Z38	IN-JCZ38	IN-HGW87	IN-MLA84	IN-MYX98	IN-N7969	Reference
Cyantraniliprole 100 g/L OD	Potato	2 × 12.5	Pre-flowering sprays	Nectar	na	na	na	na	na	na	na	DuPont-30546
				Pollen	*	*	*	*	*	*	*	
Cyantraniliprole 100 g/L OD	Potato	2 × 12.5	Pre-flowering sprays	Nectar	*	*	*	*	*	*	*	DuPont-30547
				Pollen	*	*	*	*	*	*	*	
Cyantraniliprole 100 g/L OD	Grapevine	1 × 112.5	Pre-flowering spray	Nectar	**9.8**	*	*	*	*	*	*	DuPont-30549
				Pollen	**769.7**			5.2		7.3		
Cyantraniliprole 100 g/L OD	Melon	2 × 90	Pre-flowering sprays	Nectar	*	*	*	*	*	*	*	DuPont-30553
				Pollen	**78.32**	*	*	*	*	*	*	
Cyantraniliprole 100 g/L OD	Melon	2 × 90	Pre- and flowering spray	Nectar	**13.4**	*	*	*	*	*	*	DuPont-30543
				Pollen	**97**	*	*	*	*	*	*	

Cyantraniliprole 100 g/L OD + codacide oil	Melon	1 × 120	Pre- and Flowering spray	Nectar	**31.3**	*	*	*	*	*	*	DuPont-27846, Rev No. 2
				Pollen	**86.8**	6.3	*	*	*	*	*	
Cyantraniliprole 100 g/L OD + codacide oil	Oilseed rape	1 × 120	Pre- and flowering spray	Nectar	**38.5**	*	*	*	*	*	*	DuPont-27845, Rev No. 2
				Pollen	**1933**	25.3	*	28.3	*	15.5	*	
Cyantraniliprole 100 g/L OD + codacide oil	Tomato	2 × 90	Pre- and flowering spray	Nectar	**na**	na	na	na	na	na	na	DuPont-30544
				Pollen	**211.5**	*	*	*	15.7	*	*	
Cyantraniliprole 100 g/L OD + codacide oil	Tomato	2 × 90	Early growth stage spray	Nectar	**na**	na	na	na	na	na	na	DuPont-30545
			Pre-flowering spray	Pollen	**103.1**	*	*	*	*	*	*	
Cyantraniliprole 100 g/L SE	Olives	1 × 50	Pre-flowering spray	Nectar	**na**	na	na	na	na	na	na	DuPont-30030
Cyantraniliprole 100 g/L SE				Pollen	**1607**	10	*	12.2	*	12.6	*	
Cyantraniliprole 100 g/L SE	Olives	1 × 50		Nectar	**na**	na	na	na	na	na	na	DuPont-30031

Cyantraniliprole 100 g/L SE			Pre-flowering spray	Pollen	**189.7**	*	*	*	*	*	*	
Cyantraniliprole 100 g/L SE	Grapevine	1 × 112.5	Pre-flowering spray	Nectar	**139.5**	*	*	*	*	*	*	DuPont-30548
				Pollen	**491**	10.2	*	*	*	5.3	*	
Cyantraniliprole 100 g/L SE + codacide oil	Citrus	2 × 150	Pre-flowering spray	Nectar	**132.2**	*	*	*	*	*	*	DuPont-30029
				Pollen	**107.8**	5.5	*	*	*	*	*	
Cyantraniliprole 100 g/L SE + codacide oil	Citrus	1 × 150	Pre-flowering spray	Nectar	**836.5**	12.5	*	*	*	*	*	DuPont-27848, Rev 3
				Pollen	**2505**	*	*	*	*	5.6	*	
Cyantraniliprole 100 g/L SE + codacide oil	Citrus	2 × 150	Pre-flowering spray	Nectar	**40.8**	*	*	*	*	*	*	DuPont-30028, Rev. 1
				Pollen	**1210**	39.4	*	5.3	*	*	*	
Cyantraniliprole 100 g/L SE + codacide oil	Nectarine	1 × 100	Pre-flowering spray	Nectar	**47**	*	*	*	*	*	*	DuPont-30026, Rev. 1
				Pollen	**3450**	*	*	16.6	*	15	*	
Cyantraniliprole 100 g/L SE + codacide oil	Nectarine	1 × 100	Flowering spray	Nectar	**145.8**	*	*	*	*	*	*	DuPont-30027
				Pollen	**2915**	*	*	*	*	*	*	
	Apple	1 × 150		Nectar	**14.2**	*	*	*	*	*	*	

Cyantraniliprole 100 g/L SE + codacide oil			Pre flowering spray	Pollen	**1454**	*	*	7.6	*	5.9	*	DuPont-27847, Rev. 2
Cyantraniliprole 100 g/L SE + codacide oil	Apple	1 × 150	Pre flowering spray	Nectar	**107.3**	*	*	*	*	*	*	DuPont-28266
				Pollen	**1588**	10.1	*	6.3	*	5.3	*	

Note that many of the tests conducted with other non-target arthropods also included the spray additive Codacide oil which is not specified for use with these products under New Zealand conditions.

In the absence of test data on the formulations alone, the results from those tests have also been summarised below. This is particularly the case for the parasitic wasp, *Aphidius rhopalosiphi* and the higher tier studies, where exclusion of the data would result in large gaps in information.

Table 29 Terrestrial invertebrate toxicity – other non-target arthropods, laboratory, semi-field and field studies

Test species	Test type, duration. endpoint	Formulations	
		Benevia	**Exirel**
Predatory mite, *Typhlodromus pyri*	**7 day** LR_{50} laboratory glass plate	**LR_{50} >2300 mL product/ha (>230 g ai/ha)**	
	7 day LR_{50} **and 14 day** ER_{50} laboratory glass plate		**7-day LR_{50} and 14-day ER_{50} (reproduction) >3000mL product/ha (>300 g ai/ha)**
Predatory mite populations	Field study in grape vineyards,		Exirel + Codacide oil - two applications of 1485 mg product/ha (150 g ai/ha) + 2500 mL Codacide oil applied at 14 day interval – vineyards in Italy and Germany (Italy BBCH stages 61 and 71); Germany BBCH stages 74-75) Italy – natural predatory mite populations comprised 98.2% *Kampimodromus aberrans*, 0.5% *Amblyseius andersonii,* 1.4% *Typhlodromus phialatus* No statistically significant reduction in mite predatory mite populations relative to controls. Maximum reduction in population was 19.0% Germany - natural predatory mite populations comprised 99.6% *Typhlodromus pyri* 0.4% *Euseius finlandicus*. No statistically significant reduction in predatory mite populations relative to controls. Maximum reduction in population was 20.6%.

Test species	Test type, duration. endpoint	Formulations	
		Benevia	**Exirel**
Parasitic wasp, *Aphidius rhopalosiphi*	48 hr LR_{50} laboratory glass plate	**LR_{50} 1.019 mL product/ha (0.1019 g ai/ha) nominal**	**LR_{50} 0.95 mL product/ha (0.095 g ai/ha) nominal**
	48 hr LR_{50} and ER_{50} Extended laboratory dry residues on barley	8.22 mL product/ha (0.822 g ai/ha) nominal. no repellent effect relative to controls ER_{50} for reproduction could not be determined due to mortality at the higher rate. At lower rate (1.23 mL product/ha) reproduction was significantly reduced by 21.5% and also a low level (<50%) of behavioural effects at 48 hours. NOEC <1.23 mL/ha	
	48 hr LR_{50} and ER_{50} Extended laboratory dry aged residues on barley	1 L/ha Benevia + 2.5L Codacide oil – 2 applications at 7-day interval 1st bioassay (day of 2nd application): 87% mortality of adults exposed to freshly dried residues 2nd bioassay (13 days after 2nd application): 28.2% adult mortality; reproduction not significantly different to controls 3rd bioassay (27 days after 2nd application: 5.3% mortality – not significant relative to controls; reproduction 40.5% reduced compared to controls. No repellent effects observed in any bioassay	48 hr LR_{50} 20.6 mL Exirel (2.06 g ai/ha) + 34.4 mL Codacide oil 48 hr ER_{50} > 8 mL Exirel/ha + 13.4 mL Codacide oil/ha for reduction of parasitisation No repellent effect observed; behavioural abnormalities observed at highest application rate 200 mL Exirel + 334 mL Codacide oil at 24 and 48 hour observation points In a second study at lower application rates the 48 hour LR_{50} and ER_{50} could not be determined, but 48 hour mortality was >50% at 44 ml Exirel/ha + 73.3 mL Codacide oil/ha. Based on reproductive effects the ER_{50} < 22 mL Exirel/ha + 36.7 mL Codacide oil/ha – the lowest rate tested
	Extended laboratory study on mummies,	Four nominal concentrations Benevia + Codacide oil 250 , 500, 1000, 1500 mL Benevia 417, 834, 1667, 2500 ml Codacide oil	

Test species	Test type, duration. endpoint	Formulations	
		Benevia	**Exirel**
	direct overspray	Adult hatching rate for 1-2 and 3-4 day old mummies were not affected by direct overspray up to and including the maximum application rate In the 1-2 day old mummies – variability in parasitisation rates were observed; effects on reproduction not clearly treatment related up to the maximum rate In the 3-4 day-old mummies, a rate-related decrease in reproduction occurred, and at the three highest rates was significantly different to controls. A 38.5% reduction in reproduction occurred at 1500 mL Benevia/ha. **Study rated as reliable with restrictions** by UK reviewer. No toxic reference used to demonstrate sensitivity of the test system. However, the methodology seems appropriate to test the route of exposure on adult emergence and subsequent reproduction	
	48 hour Extended laboratory exposure, field-aged residues on apple foliage		Exirel + Codacide oil – two applications at 1485 mL product (150 g ai/ha)+ 2500 mL codacide at 7 day interval 1st bioassay (directly after 2nd application): 92.5% mortality 2nd bioassay (14 DAA) and 3rd bioassay (28 DAA): no statistically significant effects on mortality or reproduction relative to controls. Second study;

Test species	Test type, duration. endpoint	Formulations	
		Benevia	**Exirel**
			Exirel + Codacide oil – one application at five test rates 7, 13, 19.5, 26 and 32.6 g ai/ha + 116.7, 216.7, 325, 433, 543 ml codacide oil respectively 1st bioassay (fresh-dried): LR_{50} 19.5 g ai/ha + 330 mL Codacide oil; ER_{50} >19.5 g ai/ha + 330 mL 2nd bioassay (2 DAA) and 3rd bioassay (7 DAA): some increased mortality and reduction in reproduction but overall ER_{50} >19.5 g ai/ha + 330 mL codacide oil
	Semi-field 48 hour exposure to freshly dried residues on barley plants	Benevia only – two test rates used 60 mL and 120 mL product/ha at 60 mL product/ha (6 g ai/ha): No statistically significant effect on parasitism at 120 mL product/ha (12 g ai/ha):**81.3%** reduction in reproduction Benevia + Codacide oil – three test rates used 60 , 120 and 180 mL product/ha + 166.7, 333.3 and 500 mL Codacide/ha respectively At all three test rates; statistically significant reduction in reproduction 59.9 – 99.5%	Exirel + Codacide oil – five test rates used 30, 60, 90, 120, 1809 mL product/ha + 50, 100, 150, 200, 300 mL codacide oil/ha At all test rates: statistically significant effects on parasitism (90.7 – 100%)
	Semi-field 48 hour exposure to freshly dried residues on barley plants	Benevia + Codacide oil – one application at 22 mL product/ha (2.2 g ai/ha) + 36.7 mL codacide oil/ha Parasitism rate not affected compared to control under semi-field conditions	

Test species	Test type, duration. endpoint	Formulations	
		Benevia	**Exirel**
Ladybird beetle, *Coccinella septempunctata*	Extended lab, fresh residues on bean leaves	19-day LR_{50} 615 mL product/ha (61.5 g ai/ha) No effects on reproduction up to 600 mL product/ha the highest rate not substantially affected by mortality	19-day LR_{50} 433 mL product/ha (43.3 g ai.ha) No effects on reproduction up to 250 mL product/ha (25 g ai/ha) the highest rate not substantially affected by mortality
	Extended laboratory, aged residue	Benevia + Codacide oil 1 L product/ha + 2.5 L Codacide oil - two applications at 7 day interval 1st bioassay (on day after 2nd application): 66.7% mortality 2nd bioassay (14 DAA) and 3rd bioassay (28 DAA) - <50% effect on reproduction relative to controls; maximum mortality 2.6%	
Green lacewing, *Chrysoperla carnea*	Extended laboratory, residues on bean leaves	19-day LR_{50} 2609 mL product/ha (260.9 g ai/ha). No adverse effects on reproduction up to and including 1260 mL product/ha – the highest rate not substantially affected by mortality	19-day LR_{50} 2126 mL product/ha (212.6 g ai/ha) No adverse effects on reproduction up to and including 1731 mL product/ha – the highest rate not substantially affected by mortality

Classification of cyantraniliprole, Benevia and Exirel for terrestrial invertebrate toxicity

Cyantraniliprole is classified as 9.4A very ecotoxic to terrestrial invertebrates, based on data derived from the formulations. Both the honey bee oral and contact toxicity tests using the active alone were inconclusive i.e. no definitive LD_{50} values were obtained (both 'greater than" values) due to the highest dose tested being too low.

Benevia is classified as 9.4B ecotoxic to terrestrial invertebrates for both oral and contact exposure based on honeybee data on the formulated product.

Exirel is classified as 9.4B ecotoxic to terrestrial invertebrates for oral exposure based on honeybee data on the formulated product.

Appendix B: Staff risk and benefit assessment

The EPA staff have evaluated the potential of Benevia and Exirel to cause adverse effects during all stages of the substance's lifecycle.

Quantitative assessments have been undertaken for the use phase of the substance's lifecycle. Qualitative assessments have been undertaken for all other stages of the lifecycle. In these cases, the level of risk has been evaluated on the basis of the magnitude and likelihood of adverse effects occurring to people or the environment.

The process by which the risk assessment of substances is undertaken is specified in the Methodology[15]. Guidance on risk assessment is provided on the EPA website[16].

To facilitate the assessment of risks the applicant and the staff identified the most common potential sources of risk to the environment and to human health and safety through release, spillage or exposure throughout the lifecycle of the substance. These are tabulated in Table 30.

Table 30 Potential sources of risks associated with hazardous substances

Lifecycle Activity	Associated Source of Risk
Manufacture* / Import	An incident during the manufacture or importation of the substance resulting in spillage and subsequent exposure of people or the environment to the substance
Packing*	An incident during the packing of the substance resulting in spillage and subsequent exposure of people or the environment to the substance
Transport or storage	An incident during the transport or storage of the substance resulting in spillage and subsequent exposure of people or the environment to the substance
Use	Application of the substance resulting in exposure of users or bystanders or the environment; or an incident during use resulting in spillage and subsequent exposure of users or the environment to the substance
Disposal	Disposal of the substance or packaging resulting in exposure of people or the environment to the substance

* The applicant intends to import (not manufacture) Benevia and Exirel. However, it is possible that the substance could be manufactured in New Zealand in the future. Consequently, the risks associated with the manufacture of Benevia and Exirel have been evaluated so the approval of this substance will be applicable to both the import and manufacture Benevia and Exirel

[15] http://www.epa.govt.nz/publications/methodology.pdf
[16] http://www.epa.govt.nz/Publications/ER-TG-05-02-03-09-(Decision-Making).pdf

Quantitative worker (operator) risk assessment

Critical endpoint definition

AOEL

Has an AOEL already been set by an internationally reputable regulatory authority accepted by EPA?

☐ Yes ☒ No

Deriving an AOEL for cyantraniliprole

Table 31 Cyantraniliprole AOEL derivation

Key systemic effect	NOAEL mg/kg bw/day	Uncertainty factors	Absorption factor[17]	AOEL mg/kg bw/day	Justification
90-day mouse: Liver toxicity (focal necrosis and increase liver weights)	150	100	1.0	1.5	The NOAEL is higher than that in the 90-day studies in rats and dogs
90-day rat: Thyroid follicular cell hypertrophy	7	100	1.0	0.07	The NOAEL is higher than that in the 90-day study in dogs
90-day dog: Liver toxicity (changes in clinical chemistry at LOAEL)	**3**	**100**	**1.0**	**0.03**	**The NOAEL in the 90-day toxicity study in dogs was lower than those in the 90-day studies in rats and mice. This is the most sensitive endpoint and is considered protective against the thyroid effects seen in the rat study**
90-day neurotoxicity study – rat: No adverse effects	1195	100	1.0	11.95	No adverse effects observed
90-day mechanistic study	1230	100	1.0	12.3	No adverse effects observed

[17] $\frac{\%Absorption}{100}$

(adrenal and thyroid) – rat: No adverse effects					
90-day mechanistic study (adrenal) – mouse: No adverse effects	1120	100	1.0	11.2	No adverse effects observed

A default oral absorption factor of 1 (i.e. 100% absorption) was used: information on absorption was not available from the sub-chronic toxicity studies, however ADME studies with cyantraniliprole indicate that it is readily absorbed following oral administration.

Other inputs for human worker (operator) and re-entry exposure modelling[18]

Table 32 Derivation of dermal absorption value in humans

Formulation	Active	Physical form	Concentration of each active (g/L or g/kg)	Maximum application rate (for each active, for each method of application) g a.i./ha	Dermal absorption (%)		AOEL mg/kg bw/day
					Concentrate	Spray	
Benevia	Cyantraniliprole	Liquid	100 g/L	50 g a.i./ha	0.1	0.1	0.03
Exirel	Cyantraniliprole	Liquid	100 g/L	15	0.25	1	0.03

[18] The Staff has undertaken an assessment of risks to operator health using the United Kingdom Pesticide Safety Directorate's interpretation of the German BBA Model to estimate operator exposure. This model estimates the exposure of workers to a pesticide during mixing, loading and during spray application, in mg/kg person/day (http://www.pesticides.gov.uk/index.htm). The derived values consider both dermal and inhalation exposure routes. The Staff typically uses the geometric mean model. The BBA model provides for a range of different spray applications (tractor-mounted/trailed sprayers and hand-held sprayers) and formulation types (liquid, wettable powder and wettable granule). Additionally, the BBA model also allows flexibility to vary protective clothing (hands, head and body).

Comments on inputs for human worker (operator) exposure modelling input parameters:

Benevia

Dermal absorption studies were provided by the applicant for the concentrate and the aqueous solution (1g cyantraniliprole/L aqueous dilution). Studies covered rat absorption *in vivo* and rat and human *in vitro* dermal absorption. Dermal absorption was calculated using the following formula:

In vivo human absorption = (*in vivo* rat absorption) X [(*in vitro* human absorption) / (*in vitro* rat absorption)]

- For the concentrate, the values used were: 1.36 X [0.3/10.5] = 0.04
- For the aqueous solution, the values used were: 0.74 X [0.86/20.2] = 0.03

These values were rounded to 0.1 for the risk assessment.

Exirel

Dermal absorption studies were provided by the applicant for the concentrate and the aqueous solution (1g cyantraniliprole/L aqueous dilution). Studies covered rat absorption *in vivo* and rat and human *in vitro* dermal absorption. Dermal absorption was calculated using formula above:

- For the concentrate, the values used were: 1.25 X [2.7/13.4] = 0.25
- For the aqueous solution, the values used were: 1.47 X [6.07/10.7] = 0.83

The value for the aqueous solution was rounded to 1 for the risk assessment.

Output of human worker (operator) mixing, loading and application exposure modelling –Benevia

Table 33 Worker mixing, loading and application exposure -Benevia

Exposure Scenario	Estimated operator exposure (mg/kg bw/day)	Risk Quotient
Boom		
No PPE[19] during mixing, loading and application	0.000086	0.0029
Gloves only during mixing and loading	0.000052	0.0017
Gloves only during application	0.000081	0.0027
Full PPE during mixing, loading and application (excluding respirator)	0.000024	0.0008
Full PPE during mixing, loading and application (including respirator)	0.000002	0.0001

[19] Full" PPE includes: gloves, hood/visor, coveralls, and heavy boots during application. The model only provides for use of gloves at mixing loading.

Outcomes of the worker (operator) exposure assessment – Benevia

- Exposure modeling for Benevia was not performed for airblast or backpack application as these application methods were not included in the GAP table submitted.
- No PPE is recommended as necessary to reduce the risk from Benevia to an acceptable level during mixing, loading, and application[20].....☒

Output of the re-entry exposure assessment – Benevia:

Table 34 Re-entry exposure modeling[21] - Benevia

Active	Internal (absorbed) dose available for systemic distribution (mg/kg bw/8 hours)	AOEL (mg/kg bw/day)	Risk Quotient at 24 hours
Cyantraniliprole	0.000081	0.03	0.0027

Outcomes of the re-entry exposure – Benevia

- No re-entry control is recommended as necessary to reduce the level of re-entry risk from Benevia.

Output of human worker (operator) mixing, loading and application exposure modelling – Exirel

Table 35 Worker mixing, loading and application exposure - Exirel

Exposure Scenario	Estimated operator exposure (mg/kg bw/day)	Risk Quotient
Boom		
No PPE[22] during mixing, loading and application	0.000120	0.0040
Gloves only during mixing and loading	0.000095	0.0032
Gloves only during application	0.000104	0.0035
Full PPE during mixing, loading and application (excluding respirator)	0.000011	0.0004

[20] The Staff consider that, while the 'no PPE' exposure model leads to an acceptable level of risk, it is appropriate to retain requirements for PPE since the use of PPE when handling agrichemicals is good practice. The Staff note that the HSNO PPE requirements are not prescriptive allowing users to select an appropriate level of PPE.

[21] The Staff assessed the re-entry worker exposures using the generic exposure model for "Maintenance and harvesting activities: Dermal exposure" provided by the UK Health & Safety Executive chemical Regulation Directorate, on the following web site: http://www.pesticides.gov.uk/applicant_guide.asp?id=1246&link=%2Fuploadedfiles%2FWeb%5FAssets%2FPSD%2FRe%2Dentry%2520worker%2520guidance%5Ffinal%2520version%2Epdf.

[22] Full" PPE includes: gloves, hood/visor, coveralls, and heavy boots during application. The model only provides for use of gloves at mixing loading.

Full PPE during mixing, loading and application (including respirator)	0.000004	0.0001

Outcomes of the worker (operator) exposure assessment – Exirel

- Exposure modeling for Exirel was not performed for airblast or backpack application as these application methods were not included in the GAP table submitted.
- No PPE is recommended as necessary to reduce the risks from Exirel to an acceptable level during mixing, loading, and application[23].....☒
-

Output of the re-entry exposure assessment – Exirel:

Table 36 Re-entry exposure modeling[24] -Exirel

Active	Internal (absorbed) dose available for systemic distribution (mg/kg bw/8 hours)	AOEL (mg/kg bw/day)	Risk Quotient at 24 hours
Cyantraniliprole	0.00018	0.03	0.006

Outcomes of the re-entry exposure – Exirel

- No re-entry control is recommended as necessary to reduce the level of re-entry risk from Exirel.

Quantitative bystander risk assessment[25]

Critical endpoints definition

The AOEL derived for operator and re-entry worker assessment above is also used for the bystander assessment calculations.

[23] The Staff considers that, while the 'no PPE' exposure model leads to an acceptable level of risk, it is appropriate to retain requirements for PPE since the use of PPE when handling agrichemicals is good practice. The Staff notes that the HSNO PPE requirements are not prescriptive allowing users to select an appropriate level of PPE.
[24] The Staff assessed the re-entry worker exposures using the generic exposure model for "Maintenance and harvesting activities: Dermal exposure" provided by the UK Health & Safety Executive chemical Regulation Directorate, on the following web site:
http://www.pesticides.gov.uk/applicant_guide.asp?id=1246&link=%2Fuploadedfiles%2FWeb%5FAssets%2FPSD%2FRe%2Dentry%2520worker%2520guidance%5Ffinal%2520version%2Epdf
[25] The Staff consider that the main potential source of exposure to the general public for substances of this type (other than via food residues which will be considered as part of the registration of this substance under the Agricultural Compounds and Veterinary Medicines (ACVM) Act 1997) is via spray drift. In terms of bystander exposure, toddlers are regarded as the most sensitive sub-population and are regarded as having the greatest exposures. For these reasons, the risk of bystander exposure is assessed in this sub-population. The EPA has agreed that the AOEL used for operator and re-entry worker exposure assessment should be used for the bystander assessment, as the use of an oral chronic reference dose (CRfD) is usually likely to be over-precautionary.

Output of human bystander mixing, loading and application exposure modelling - Benevia[26]

Table 37 Bystander mixing, loading and application exposure modelling - Benevia

Exposure Scenario	Estimated exposure of 15 kg toddler exposed through contact to surfaces 8 m from an application area (µg/kg bw/day)	Risk Quotient
Boom		
High boom, fine droplets	0.17	0.0055
High boom, coarse droplets	0.03	0.0009
Low boom, fine droplets	0.06	0.0019
Low boom, coarse droplets	0.01	0.0004

Outcomes of the bystander exposure assessment - Benevia

- Bystander exposure modeling for Benevia was not performed for airblast or aerial application as these application methods were not included in the GAP table submitted.
- The risks to bystanders from Benevia are acceptable..... ☒

[26] Exposure is estimated using the equations from the UK Health & Safety Chemical Regulation Directorate which account for dermal exposure, hand-to-mouth exposure and object-to-mouth exposure (http://www.pesticides.gov.uk/uploadedfiles/Web_Assets/PSD/Bystander%20exposure%20guidance_final%20version.pdf Accessed 27/01/2010a). In addition, incidental ingestion of soil is taken into account using a modified exposure equation from the United States Environmental Protection Agency (USEPA, 2007, Standard Operating Procedures (SOPs) for Residential Exposure Assessments, Contract No. 68-W6-0030, Work Assignment No. 3385.102). Spray drift is estimated using models specific to the type of application equipment. For pesticides applied by ground boom or air blast sprayer, the AgDrift model is used. Spray drift deposition from aerial application is estimated using the AGDISP model along with appropriate New Zealand input parameters

Output of human bystander mixing, loading and application exposure modelling - Exirel[27]

Table 38: Bystander mixing, loading and application exposure modelling - Exirel

Exposure Scenario	Estimated exposure of 15 kg toddler exposed through contact to surfaces 8 m from an application area (µg/kg bw/day)	Risk Quotient
Boom		
High boom, fine droplets	0.045	0.0015
High boom, coarse droplets	0.007	0.0002
Low boom, fine droplets	0.015	0.0005
Low boom, coarse droplets	0.004	0.0001

Outcomes of the bystander exposure assessment - Exirel

- Bystander exposure modeling for Exirel was not performed for airblast or aerial application as these application methods were not included in the GAP table submitted
- The risks to bystanders from Exirel are acceptable..... ☒

Summary and conclusions of the human health risk assessment

For both Benevia and Exirel, the exposure modelling indicates that risks for the operator, re-entry worker and bystander under the proposed use pattern are acceptable without additional controls being applied. Nevertheless, the use of personal protective equipment during mixing, loading and application and early re-entry to treated crops is good practice.

[27] Exposure is estimated using the equations from the UK Health & Safety Chemical Regulation Directorate which account for dermal exposure, hand-to-mouth exposure and object-to-mouth exposure (http://www.pesticides.gov.uk/uploadedfiles/Web_Assets/PSD/Bystander%20exposure%20guidance_final%20version.pdf Accessed 27/01/2010a). In addition, incidental ingestion of soil is taken into account using a modified exposure equation from the United States Environmental Protection Agency (USEPA, 2007, Standard Operating Procedures (SOPs) for Residential Exposure Assessments, Contract No. 68-W6-0030, Work Assignment No. 3385.102). Spray drift is estimated using models specific to the type of application equipment. For pesticides applied by ground boom or air blast sprayer, the AgDrift model is used. Spray drift deposition from aerial application is estimated using the AGDISP model along with appropriate New Zealand input parameters

Quantitative ecological risk assessment[28]

Aquatic risk assessment

For Class 9 substances, irrespective of the intrinsic hazard classification, the ecological risk can be assessed for a substance by calculating a Risk Quotient (RQ) based on an estimated exposure concentration. Such calculations incorporate toxicity values, exposure scenarios (including spray drift, leaching and run-off, application rates and frequencies), and the half-lives of the component(s) in water. For the aquatic environment, the calculations provide an Estimated Environmental Concentration (EEC) which, when divided by the L(E)C_{50} or a NOEC, gives a RQ acute or chronic.

$$Acute\ RQ = \frac{EEC_{short-term}}{L(E)_{50}}$$

$$Chronic\ RQ = \frac{EEC_{long-term}}{NOEC}$$

If the RQ exceeds a predefined level of concern, this suggests that it may be appropriate to refine the assessment or apply the approved handler control and/or other controls to ensure that appropriate matters are taken into account to minimize off-site movement of the substance. Conversely, if a worst-case scenario is used, and the level of concern is not exceeded, then in terms of the environment, there is a presumption of low risk which is able to be adequately managed by such things as label statements (warnings, disposal). The approved handler control can then be removed on a selective basis.

Levels Of Concern (LOC) developed by the USEPA (Urban and Cook, 1986) and adopted by EPA determine whether a substance poses an environmental risk (Table).

Table 38 Levels of concern as adopted by EPA New Zealand

Endpoint	LOC	Presumption
Aquatic (fish, invertebrates)		
Acute RQ	≥ 0.5	High acute risk
Acute RQ	0.1 - 0.5	Risk can be mitigated through restricted use
Acute RQ	< 0.1	Low risk

[28] For Class 9 substances, irrespective of the intrinsic hazard classification, the ecological risk can be assessed for a substance by calculating a risk quotient based on an estimated exposure concentration. Such calculations incorporate toxicity values, exposure scenarios (including spray drift, application rates and frequencies), and the half-lives of the component(s) in soil and water. The calculations provide an Estimated Environmental Concentration (EEC) which, when divided by the LC_{50} or EC_{50}, gives a risk quotient (RQ).

Chronic RQ	≥ 1	High chronic risk
Plants (aquatic and terrestrial)		
Acute RQ	≥ 1	High acute risk

GENEEC2 modelling

Calculation of expected environmental concentrations

The parameters used in GENEEC2 modelling are listed in Table

Table 39 Input parameters for GENEEC2 analysis

Cyantraniliprole	**1** **Fodder brassicas**	**2** **Onions, potatoes, field tomatoes**
Application rate (g/ha)	15	50
Application frequency	3	3
Application interval (days)	14	7
Kd [lowest non-sand value]	2.77	
Aerobic soil DT_{50} (days)	43.7	
Pesticide wetted in?	no	
Methods of application	Ground, high boom, medium droplet	
'No spray' zone	nil	
Water solubility (ppm)	14.24	
Hydrolysis (DT_{50} in days)	pH 4 261 **pH 7 61**	
Aerobic aquatic $DT_{50\ whole\ system}$(days) [GENEEC – longest]	25.1	
Aqueous photolysis DT_{50} (days)	0.22	

Output from the GENEEC2 model

Scenario1 – fodder brassicas

```
RUN No.   1 FOR cyantraniliprole ON   fodder bra    * INPUT VALUES *
---------------------------------------------------------------------
RATE (#/AC)   No.APPS &   SOIL  SOLUBIL   APPL TYPE  NO-SPRAY INCORP
 ONE(MULT)    INTERVAL     Kd   (PPM )    (%DRIFT)   ZONE(FT)  (IN)
```

.013(| .033)	3	14	2.8	14.2	GRHIME(1.2)	.0	.0

FIELD AND STANDARD POND HALFLIFE VALUES (DAYS)

METABOLIC (FIELD)	DAYS UNTIL RAIN/RUNOFF	HYDROLYSIS (POND)	PHOTOLYSIS (POND-EFF)	METABOLIC (POND)	COMBINED (POND)
43.70	2	N/A	.22- 27.28	25.10	13.07

GENERIC EECs (IN MICROGRAMS/LITER (PPB)) Version 2.0 Aug 1, 2001

PEAK GEEC	MAX 4 DAY AVG GEEC	MAX 21 DAY AVG GEEC	MAX 60 DAY AVG GEEC	MAX 90 DAY AVG GEEC
1.26	1.20	**.95**	.59	.44

Scenario 2 – onions, potatoes, field tomatoes

RUN No. 2 FOR cyantraniliprole ON field veg * INPUT VALUES *

RATE (#/AC) ONE(MULT)	No.APPS & INTERVAL	SOIL Kd	SOLUBIL (PPM)	APPL TYPE (%DRIFT)	NO-SPRAY ZONE(FT)	INCORP (IN)
.045(.120)	3	7	2.8	14.2	GRHIME(1.2)	.0	.0

FIELD AND STANDARD POND HALFLIFE VALUES (DAYS)

METABOLIC (FIELD)	DAYS UNTIL RAIN/RUNOFF	HYDROLYSIS (POND)	PHOTOLYSIS (POND-EFF)	METABOLIC (POND)	COMBINED (POND)
43.70	2	N/A	.22- 27.28	25.10	13.07

GENERIC EECs (IN MICROGRAMS/LITER (PPB)) Version 2.0 Aug 1, 2001

PEAK GEEC	MAX 4 DAY AVG GEEC	MAX 21 DAY AVG GEEC	MAX 60 DAY AVG GEEC	MAX 90 DAY AVG GEEC
4.63	4.43	**3.48**	2.17	1.62

The maximum Estimated Environmental Concentrations (EEC) for cyantraniliprole when used in Benevia and Exirel as estimated by GENEEC2 is:

- 1.26 µg/L for scenario 1 (Fodder brassicas - Exirel) and
- 4.63 µg/L for scenario 2 (onions, potatoes, field tomatoes - Benevia).

Calculation of acute risk quotients using GENEEC2 expected environmental concentrations

Table 40 gives calculated acute risk quotients for each trophic level considering EEC estimated by GENEEC2 and lowest relevant toxicity figures for the most sensitive species.

Table 40 Acute risk quotients derived from the GENEEC2 model and toxicity data

Species	Peak EEC from GENEEC2 (mg/L)	LC_{50} or EC_{50} (mg/L)	Acute RQ	Presumption
Scenario 1 - Fodder brassicas (Exirel)				
Fish , Rainbow trout	0.00126	2.4 mg ai/L (tested as Benevia)	0.0005	Low risk
Crustacea, *Daphnia magna*		0.0185 mg ai/L (tested as Exirel)	0.007	
Algae, *Pseudokirschneriella subcapitata*		3.39 mg ai/L (tested as Exirel)	0.0004	
Scenario 2 - onion, potatoes, field tomatoes (Benevia)				
Fish , Rainbow trout	0.00463	2.4 mg ai/L (tested as Benevia)	0.002	Low risk
Crustacea, *Daphnia magna*		0.00947 (tested as Benevia)	0.49	**Risk requires mitigation**
Algae, *Pseudokirschneriella subcapitata*		6.62 mg ai/L (tested as Benevia)	0.0007	Low risk

Conclusion for the acute aquatic risk assessment using GENEEC2 data

The proposed use of Exirel presents a low acute risk to aquatic organisms.

The proposed use of Benevia presents an acute risk to aquatic organisms and requires mitigation.

Calculation of chronic risk quotients using GEENEC2 expected environmental concentrations

Table gives calculated chronic risk quotients for each trophic level considering EEC estimated by GENEEC2 and lowest relevant toxicity figures.

Table 41 Chronic risk quotients derived from the GENEEC2 model and toxicity data

Species	Relevant EEC from GENEEC2 (µg /L)*	NOEC (µg/L)	Chronic RQ	Presumption
Scenario 1 – Fodder brassicas (Exirel)				
Fish, rainbow trout,	90-day EEC 0.44	90 day –ELS 1010	0.0004	**Low risk**
Crustacea ,*Daphnia magna*	21-day EEC 0.95	21-day repro 6.56	0.14	
Scenario 2 – Onions, potatoes, field tomatoes (Benevia)				
Fish, rainbow trout	90 day EEC 1.62	90 day –ELS 1010	0.002	**Low risk**
Crustacea ,*Daphnia magna*	21-day EEC 3.48	21-day repro 6.56	0.53	

* EEC selected must be as close as possible from the exposure duration of the study selected for risk assessment purpose.

Conclusion for the chronic aquatic risk assessment using GENEEC2 data

Cyantraniliprole, applied as the formulated products Benevia and Exirel, presents a low chronic risk to the aquatic environment under the proposed use scenarios.

AgDRIFT® modelling

AgDRIFT® modelling does not allow determining EEC *per se*. AgDRIFT® modelling output is a buffer zone determination to be respected in order to get a risk quotient < 1. There is no risk quotient >1 so the modelling was not performed.

Sediment risk assessment

Sediments may act as both a sink for chemicals through sorption of contaminants to particulate matter, and a source of chemicals through resuspension. Sediments integrate the effects of surface water contamination over time and space, and may thus present a hazard to aquatic communities (both pelagic and benthic) which is not directly predictable from concentrations in the water column.

When results from whole-sediment tests with benthic organisms are available the PNECsed has to be derived from these tests using assessment factors. However, the available sediment tests should be carefully evaluated. Special attention should be given to the pathways through which the test organisms are

exposed to the chemical and the test protocol should carefully be checked to determine whether feeding with unspiked food has possibly reduced exposure *via* sediment ingestion. For assessing the toxicity of spiked sediment it is necessary to address adequately all possible routes of exposure. Sediment organisms can be exposed *via* their body surfaces to substances in solution in the overlying water and in the pore water and to bound substances by direct contact or *via* ingestion of contaminated sediment particles. The route that is most important is strongly influenced by species-specific feeding mechanisms and the behaviour of the organism in, or on, the sediment. Test design parameters can have a bearing on the route of uptake of a substance.

The PNECsed is derived from the lowest available NOEC/EC_{10} obtained in long-term tests by application of the following assessment factors and is then expressed as mg/kg of dry sediment:

Table 42 Assessment factors for derivation of PNECsed

Available test result	Assessment factor
One long-term test (NOEC or EC_{10})	100
Two long-term tests (NOEC or EC_{10}) with species representing different living and feeding conditions	50
Three long-term tests (NOEC or EC_{10}) with species representing different living and feeding conditions	10

Using the 28-day chronic reproductive NOEC from the midge (*Chironomus riparius*) spiked sediment (0.0190 mg ai/kg sediment), and dividing an assessment factor of 100, the calculated $PNEC_{sed}$ is 0.000190 mg/kg dry sediment.

PEC_{local} for sediment can be compared to the PNEC for sediment dwelling organisms. The concentration in freshly deposited sediment is taken as the PEC for sediment, therefore, the properties of suspended matter are used. The concentration in bulk sediment can be derived from the corresponding water body concentration, assuming a thermodynamic partitioning equilibrium (see also Di Toro *et al.*, 1991):

$$PEC_{localsed} = \frac{KP_{susp-water}}{RHO_{susp}} \; x \; PEC_{localwater} \; x \, 1000$$

Where

$PEC_{localwater}$ concentration in surface water during release episode based on GENEEC2 modelling

- Scenario 1: 21-day EEC 0.00095 mg/L)
- Scenario 2: 21-day EEC 0.00348 mg/L

$K_{susp-water}$ suspended matter-water partitioning coefficient = 5.65 (m^3/m^3). Equation R.16-7 of REACH TGD R16.

RHO_{susp} bulk density of suspended matter = 1150 (kg/m^3) Equation R.16-16 of REACH TGD R16.

$PEC_{localsed}$ predicted environmental concentration in sediment (mg/kg)

therefore:

- Scenario1: $PEC_{localsed}$ = 0.005 mg/kg sediment
- Scenario 2: $PEC_{localsed}$ = 0.017 mg/kg sediment

The risk for sediment-dwelling organisms is assessed as the ratio $PEC_{sed}/PNEC_{sed}$.

- Scenario 1: 0.005/0.000190 = 26
- Scenario 2: 0.017/0.000190 = 89

Conclusion for the sediment risk assessment

Cyantraniliprole, applied as the formulated products Benevia and Exirel, presents a low chronic risk to the sediment dwelling organisms under the proposed use scenarios.

Terrestrial risk assessment

For terrestrial organisms, Toxicity-Exposure Ratios (TERs) are used for earthworms and birds and Hazard Quotient (HQ) are used for terrestrial invertebrates. This convention results in concern arising if a risk quotient is less than the trigger value for earthworms and more than a trigger value for terrestrial invertebrates. LOC developed by the European Union and adopted by the Staff allowing to determine whether a substance poses an environmental risk are provided in the Table .

Table 43 Levels of concern as adopted by the Staff

	Level of Concern (LOC)	Presumption
Earthworm/ Birds		
Acute TER	< 10	High risk
Chronic TER	< 5	High risk
Bees		
HQ $_{oral/contact}$	> 50	High risk
Terrestrial invertebrates		
HQ $_{in\text{-}field/off\text{-}field}$	≥2	High risk

Earthworm risk assessment

Soil Predicted Environmental Concentration (PEC) determination

Both acute and reproductive earthworm tests are static tests where the test substance is applied to the system only once at the beginning. Therefore the nominal dose levels in the test match initial concentrations in the field and thus it is appropriate to use initial PEC values (no time-weighted averages) for the acute as well as the long-term TER.

The concentration of active substance in the soil is calculated on the basis of the FOCUS (1997) document 'Soil persistence models and EU registration'

$$PEC\ one\ application\ (mg/kg\ soil) = \frac{application\ rate\ (kg\ a.i./ha)}{75\ kg\ soil}\ x\ 100$$

Soil concentrations of the active ingredient are calculated by assuming the deposition would mix into the top 5 cm of soil, and this soil would have a bulk density of 1,500 kg/m^3, i.e. the deposition expressed in mg/m^2 would mix into 75 kg of soil.

In case of multiple applications, the following formula has to be used:

$$PEC\ multiple\ applications = PEC\ one\ application\ x\ \frac{(1-e^{-nki})}{(1-e^{-ki})}$$

where:
n = number of applications
k = ln2/DT_{50} (day^{-1})
i = interval between two consecutive applications (days)
DT_{50} = half life in soil (days) Use only DT_{50} values of lab test done at 10-20 ^oC and pH between 5 and 9.
e = 2.718 (constant)

When there are DT_{50} values of several soils use GENEEC2 formula for determining the relevant DT_{50} to be used.

PEC calculation results are summarized for each scenario in Table .

Calculation of TERs

$$TER_{acute} = \frac{LD_{50}}{Estimated\ \ Environmental\ Concentration}$$

$$TER_{long-term} = \frac{NOEC}{Estimated\ \ Environmental\ Concentration}$$

The collembolan, *Folsomia candida* was more sensitive (NOEC 0.08 mg ai/kg soil) to cyantraniliprole than the earthworm (NOEC 1000 mg/kg soil, therefore it has been included in the chronic risk assessment. There are no acute data for toxicity to *Folsomia.*

Off-field values include the use of the 1.2% value for spray drift derived from the GENEEC modelling.

Table 44 Acute *in-field* TER value for earthworms

Scenarios	PEC_{one} (mg/kg soil)	LC_{50} (mg/kg soil)	TER acute	Presumption
1 Fodder brassicas- Exirel	0.02	>1000	50 000	Low risk
2 Onions, potatoes, field tomatoes – Benevia	0.07		15 000	

Given that the calculated TER values for acute in-field exposure are so high ie risk very low, the off-field TER have not been calculated.

Conclusion for earthworm acute risk assessment

Cyantraniliprole, when applied to as Benevia and Exirel, presents a low acute risk to earthworms.

Table 45 Chronic *in-field* TER value for earthworms and *Folsomia candida*

Scenarios	PEC_{multi} (mg/kg soil)	NOEC (mg/kg soil)	TER chronic	Presumption
1 Fodder brassicas- Exirel	0.05	1000 earthworm	20 472	>5 low risk
		0.08 folsomia (mortality)	**1.63**	**<5 High risk**
2 Onions, potatoes, field tomatoes – Benevia	0.18	1000 earthworm	5564	>5 low risk
		0.08 folsomia (mortality)	**0.45**	**<5 High risk**

Table 46 Chronic *off-field* TER value for earthworms and *Folsomia candida*

Scenarios	PEC_{multi} (mg/kg soil)	NOEC (mg/kg soil)	TER chronic	Presumption
1 Fodder brassicas-Exirel	0.001	1000 earthworm	1706041	>5 low risk
		0.08 folsomia (mortality)	136	
2 Onions, potatoes, field tomatoes – Benevia	0.002	1000 earthworm	463683	>5 low risk
		0.08 folsomia (mortality)	37	

Conclusion for chronic risk assessment

Cyantraniliprole, when applied as Benevia and Exirel under the proposed use scenarios, presents a high chronic risk to springtails within the application area ie in-field. However, as previously noted, a field study examining effects of cyantraniliprole on Collembolan populations indicates that while individual taxa may be affected, the class Collembola as a whole was not adversely affected.

Non-target plant risk assessment

Non target plants are non-crop plants located outside the treatment area. The proposed applications rates of for the use of Benevia (50 g ai/ha) and Exirel (15 g ai/ha) are less than those shown to cause effects in the terrestrial plant tests (>150 g ai/ha) therefore no quantitative risk assessment has been undertaken.

Conclusion for non-target plant risk assessment

Benevia and Exirel, when applied at the maximum application rate and frequency proposed in this application, presents a low risk to non-target plants.

Bird risk assessment

In the avian toxicity tests, no effects were observed up to the highest doses tested in both the acute and chronic studies therefore no quantitative risk assessment has been undertaken.

Conclusion for bird risk assessment (screening)

The proposed uses of Benevia and Exirel present a low risk to birds.

Bee risk assessment

The risk to bees is assessed as follows:

$$HQ_{bees}\ (contact\ or\ oral) = \frac{Application\ rate\ (g\ a.i./ha)}{LD_{50(contact\ or\ oral)}\ (\mu g\ a.i./bee)}$$

Calculation of HQs

Note that in the table below, the LD_{50} values used in the assessment are those available for the active ingredient when tested as the relevant formulation. No definitive values were obtained for the active ingredient alone.

The duration of the oral studies is greater than the standard 48 hour test due to increasing mortality during testing requiring extension of the test (refer to data summaries for further details).

Table 47 Acute HQs values for bees

Species	LD_{50} (µg a.s./bee)	Application rate (g a.i./ha)	Hazard Quotient	Presumption
Oral				
Apis mellifera	0.39 µg ai/bee (tested as Benevia – 72 hr LD_{50})	50 g ai/ha (Benevia)	**128**	**High risk**
	0.92 µg ai/bee (tested as Exirel – 96 hr LD_{50})	15 g ai/ha (Exirel)	16	Low risk
Contact				
Apis mellifera	1.2 µg ai/bee (tested as Benevia – 48 hr LD_{50})	50 g ai/ha (Benevia)	42	Low risk
	3.03 µg ai/bee (tested as Exirel – 48 hr LD_{50})	15 g ai/ha (Exirel)	5	

Conclusions for bee risk assessment

The HQ_{oral} value is below the trigger value of 50, indicating that Exirel presents a low oral risk to honeybees but is above 50 for Benevia indicating a high oral risk.

The $HQ_{contact}$ value is below the trigger value of 50, indicating that Benevia and Exirel present a low risk to honeybees from contact exposure.

It should be noted that some sub-lethal effects occurred in surviving bees in both the oral and contact toxicity tests. At this time, the risk assessment methodology is not available to determine the significance of those observed effects.

Likewise, in the higher tier tests with honeybees, the possibility of adverse effects cannot be excluded.

Non-target arthropod risk assessment

Where limit tests are conducted, a low risk to non-target arthropods can be concluded when the effects at the highest application rate multiplied by MAF are below 50% (ESCORT2 workshop, 2000 – p12)

A tiered approach is applied to the assessment of risks to non-target arthropods, both in-field and off-field. At Tier 1 the risks to two indicator species are assessed (parasitic wasp, *Aphidius rhopalosiphi* and predatory mite, *Typhlodromus pyri*) on the basis of laboratory studies and worst-case exposures. If the risks to these two species are high as a result of those tests, then further testing is required using more realistic exposures to residues on plants (Tier 2), and may progress to semi-field and field studies. Testing of additional species is also required. The organisms need to be exposed to the maximum application rate intended for use and account also needs to be made of exposure to multiple applications.

Tier 1 Foliar Predicted Environmental Concentrations

$$In-field\ HQ = \frac{Application\ rate\ (g\ or\ mL\ a.i./ha)\ x\ MAF\ **}{LR_{50}^{*}}$$

* application rate and LR_{50} must not differ in their units, i.e. must be related to either formulation or a.i. rates

** Multiple application factor, refer to Appendix V, p 45 of ESCORT 2 Workshop, 2000. MAF = 1 when there is just one application.

$$Off-field\ HQ = \frac{Application\ rate\ x\ MAF\ x\ (\frac{drift\ factor*}{vegetation\ distribution\ factor**})}{LR_{50}}\ x\ correction\ factor***$$

***** Overall 90th percentile drift values are presented in Appendix VI , p 46 of ESCORT 2 Workshop, 2000.

** default value of 10

*** default value of 10

Calculation of hazard quotients

The resultant in-field and off-field hazard quotients for *Aphidius rhopalosiphi* and *Typholodromus pyri* are shown in the Table 48 and Table 49.

Table 48 *In-field* HQ values for *Aphidius rhopalosiphi* and *Typholodromus pyri*

Species	LR_{50} (g ai/ha)	Application rate (g ai/ha)	MAF	Hazard Quotient	Presumption
Parasitic wasp, *Aphidius rhopalosiphi*	0.1019	50 (Benevia)	2.3	**1129**	**High risk**
	0.095	15 (Exirel)		**363**	
Predatory mite, *Typhlodromus pyri*	>230	50 (Benevia)		0.5	Low risk
	>300	15 (Exirel)		0.12	

Table 49 Off-field HQ values for Aphidius rhopalosiphi and Typholodromus pyri

Species	LR_{50} (g a.i/ha)	Application rate (g ai./ha)	MAF	Vegetation factor	Correction factor	Drift factor	Hazard Quotient	Presumption
Parasitic wasp, *Aphidius rhopalosiphi*	0.1019	50 (Benevia)	2.3	10	10	0.0277	**31**	**High risk**
	0.095	15 (Exirel)					**10**	
Predatory mite, *Typhlodromus pyri*	>230	50 (Benevia)					0.01	Low risk
	>300	15 (Exirel)					0.96	

The in-field and off-field HQ values for the parasitic wasp, *Aphidius rhopalosiphi*, are well above the trigger value of 2 in the Tier 1 assessment, indicating that the active substance cyantraniliprole is of high concern for some non-target arthropods. However, the predatory mites tested appear to be highly resistant to cyantraniliprole.

Tier 2 assessment

The applicant provided some additional test data from Tier 2 extended laboratory tests as set out in Table 50. Many of the studies provided included the use of the adjuvant Codacide oil complicating interpretation of the study results. The test results included below were undertaken on the formulated products without the addition of codacide oil.

Table 50 Tier 2 extended laboratory tests for non-target arthropods

Species	Test	Application rate (g ai/ha)	Result
Parasitic wasp, *Aphidius rhopalosiphi*	Semi-field – fresh residues on barley	12 g ai/ha without codacide oil [applied as Benevia]	Effects on reproductive capacity >50%
Green lacewing, *Chrysoperla carnea*	Extended lab – residues on bean leaves	260.9 g ai/ha (tested as Benevia)	19-day LR_{50} 260.9 g ai/ha No adverse effects on reproduction up to 1260 mL product/ha the highest rate not substantially affected by mortality
		212.6 g ai/ha (tested as Exirel)	19-day LR_{50} 212.6 gai/ha no adverse effects on reproduction up to and

Species	Test	Application rate (g ai/ha)	Result
			including 1731 mL product/ha
Ladybird beetle, *Coccinella septempunctata*	Extended lab – fresh residues on bean leaves	62.5 g ai/ha (tested as Benevia)	19-day LR_{50} 62.5 g ai/ha tested as Benevia [615 mL product/ha] No effects on reproduction up to 600 mL product/ha, the highest rate without substantial mortality
		43.3 g ai/ha (tested as Exirel)	19-day LR_{50} 43.3 gai/ha (433 mL product/ha) No effects on reproduction up to 25 g ai/ha, the highest rate not substantially affecting mortality

Benevia presents a high risk to the parasitic wasp, *Aphidius rhopalosiphi* based on >50% effects on reproduction under semi-field conditions. The equivalent data was not available for Exirel.

Reproductive effects >50% were not observed in the other species tested, indicating low chronic risk.

Conclusion for non-target arthropod risk assessments

There is wide variability in the sensitivity of non-target arthropods to cyantraniliprole. The predatory mite, *Typhlodromus pyri* is at low risk from exposure to the formulated products, whereas the parasitic wasp, *Aphidius rhopalosiphi* exhibited adverse effects under semi-field conditions and is at high risk from exposure to the substance.

The ladybird species tested exhibited significant mortality at an application rate of Benevia and Exirel higher than those proposed for New Zealand, as did the green lacewing.

Given the variability in sensitivity to cyantraniliprole amongst the non-target arthropods tested, and the absence of any relevant field studies to provide information on the recolonisation potential of affected species, the applicant's claim on the label of both products regarding integrated pest management is not supported, ie:

"*DuPont Benevia/Exirel insecticide has been specifically designed for use in Integrated Pest Management (IPM) programs. DuPont ..insecticide helps conserve beneficial arthropods. …"*

Summary and conclusions of the ecological risk assessment

Cyantraniliprole, formulated as Benevia and Exirel, when used under the scenarios addressed in the ecological risk assessment presents potential risks to the aquatic and terrestrial environments.

Aquatic environment

- Initial assessment indicates that risks posed by the use of Benevia on field vegetables require mitigation.

Terrestrial environment

- High chronic risk to soil dwelling organisms (collembola) within the application area from the use of Benevia and Exirel is indicated by the laboratory data, however, a field study examining effects on Collembola populations showed transitory effects on individual taxa, but the class as a whole was not adversely affected.
- Honeybees - Exirel presents a low oral risk to honeybees based on the standard acute risk assessment methodology and Benevia presents a high oral risk.
  Benevia and Exirel present a low acute risk to honeybees from contact exposure.

  It should be noted that some sub-lethal effects occurred in surviving bees in both the oral and contact toxicity tests. At this time, the risk assessment methodology is not available to determine the significance of those observed effects. Likewise, in the higher tier tests with honeybees, the possibility of adverse effects cannot be excluded with no standardised methodology currently available to further evaluate risks from exposure in the field. Some short-term effects on behaviour or mortality were observed in semi-field tests. Impacts on brood development were generally not observed, though it was noted that in many cases the brood assessments were only conducted once before and once after application, which is not sufficiently long enough to derive endpoints regarding colony strength and brood development.
- Bumblebees – as for honeybees, there is no risk assessment methodology available to evaluate the risks to this species. In the semi-field (greenhouse) studies undertaken with Benevia and a formulation not subject to this application there were potentially treatment related effects on queen mortality at an application rate of 10 g ai/ha which is a rate lower than either of those proposed for New Zealand use of Benevia and Exirel.
- Other non-target arthropods - Benevia presents a high risk to the parasitic wasp, *Aphidius rhopalosiphi* based on >50% effects on reproduction under semi-field conditions. The equivalent data was not available for Exirel.
  Reproductive effects >50% were not observed in the other species tested, indicating low chronic risk.
  There is wide variability in the sensitivity of non-target arthropods to cyantraniliprole. The predatory mite, *Typhlodromus pyri* is at low risk from exposure to the formulated products, whereas the parasitic wasp, *Aphidius rhopalosiphi* exhibited adverse effects under semi-field conditions and is at

high risk from exposure to the substance.

The ladybird species tested exhibited significant mortality at an application rate of Benevia and Exirel higher than those proposed for New Zealand, as did the green lacewing.

- Given the variability in sensitivity to cyantraniliprole amongst the non-target arthropods tested, and the absence of any relevant field studies to provide information on the recolonisation potential of affected species, the applicant's claim on the label of both products regarding integrated pest management, ie:
  "*DuPont (Benevia/Exirel) insecticide has been specifically designed for use in Integrated Pest Management (IPM) programs. DuPont (Benevia/Exirel.insecticide helps conserve beneficial arthropods. …"* is not supported by the data provided with the application

Identification of persistent, bioaccumulative and toxic (PBT) and very persistent and very bioaccumulative (vPvB) substances, components, contaminants, or metabolites

Table 51 Screening criteria for Persistency, Bioaccumulation, and Toxicity

Type of data	Criterion	Screening assessment
Persistence		
Ready biodegradability test	Readily biodegradable	Not P not vP
Enhanced ready biodegradability test	Readily biodegradable	Not P not vP
Specified tests on inherent biodegradability Zahn-Wellens (OECD 302B)	≥ 70 % mineralisation (DOC removal) within 7 d; log phase no longer than 3d; removal before degradation occurs below 15%; no pre-adapted inoculums	Not P
MITI II test (OECD 302C)	≥ 70% mineralisation (O_2 uptake) within 14 days; log phase no longer than 3d; no pre-adapted inoculum	Not P
Biowin 2 (non-linear model prediction) and Biowin 3 (ultimate biodegradation time) or Biowin 6 (MITI non-linear model prediction) and Biowin 3 (ultimate biodegradation time)	Does not biodegrade fast (probability <0.5), and ultimate biodegradation timeframe prediction: ≥months (value < 2.2) or Does not biodegrade fast (probability <0.5) and ultimate biodegradation timeframe prediction: ≥months (value < 2.2)	P P

Bioaccumulation		
Convincing evidence that a substance can biomagnify in the food chain (e.g. field data)	e.g. BMF > 1	B or vB, definitive assignment possible
Octanol-water partitioning coefficient (experimentally determined or estimated by QSAR)	Log Kow ≤ 4.5	Not B and not vB
Toxicity		
Short-term aquatic toxicity	EC50 or LC50 < 0.01 mg/L	T, criterion considered to be definitely fulfilled
Short-term aquatic toxicity	EC50 or LC50 < 0.1 mg/L	T
Avian toxicity (subchronic or chronic toxicity or toxic for reproduction)	NOEC < 30 mg/kg food	T

The outcome of the assessment is summarized in the Table

Table 52 PBT/vPvB assessment for Benevia and Exirel

	Yes	**No**	**Cannot be determined at this time**
Does the substance or is likely to contain PBT components?	☐ Component(s): Remarks:	☒	☐
Are the metabolites (mammalian and/or environmental) PBT?	☐ Metabolite(s): Remarks:	☒	☐
Does the substance contain or is likely to contain vPvB (POP) components?	☐ Component(s): Remarks:	☒	☐
Are the metabolites (mammalian and/or environmental) vPvB (POP)?	☐ Metabolite(s): Remarks:	☒	☐
Does the substance contain POP stipulated in the Stockholm Convention?	☐ Substance: Remarks:	☒	☐

Conclusion for PBT/vPvB assessment

Cyantraniliprole does not trigger any of the criteria for a PBT/vPvBT substance.

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Appendix C: Controls applying to Benevia and Exirel

The controls for these substances apply for the indefinite duration of the approval of these substances.

Please refer to the Hazardous Substances Regulations[36] for the requirements prescribed for each control and the modifications listed as set out in Section 6 of this document.

Table 53 Controls for Benevia – codes, regulations and variations

Hazardous Substances (Classes 6, 8, and 9 Controls) Regulations 2001

Code	Regulation	Description	Variation
T1	11 – 27	Limiting exposure to toxic substances through the setting of TELs	No TEL values are set for any components of this substance at this time. The following ADE and PDE values are set for cyantraniliprole: ADE = 0.01 mg/kg bw/day PDE_{Food} = 0.007 mg/kg bw/day PDE_{Water} = 0.002 mg/kg bw/day PDE_{Other} = 0.001 mg/kg bw/day
T2	29, 30	Controlling exposure in places of work through the setting of WESs	No Ministry of Business, Innovation and Employment (MBIE) WES exists for any components in Benevia
T4	7	Requirements for equipment used to handle substances	
T5	8	Requirements for protective clothing and equipment	
T7	10	Restrictions on the carriage of toxic or corrosive substances on passenger service vehicles[37]	Regulation 10 applies as if the maximum quantity per package of a 6.5B substance is 1.0 L, rather than 0.1 L
E1	32 – 45	Limiting exposure to ecotoxic substances through the setting of EELs	No EEL values are set for this substance at this time and the default EELs are deleted
E2	46 – 48	Restrictions on use of substances in application areas	As no EELs have been set for this substance, no application rate is required to be set. However, a maximum application rate is set under section 77A for this substance
E5	5(2), 6	Requirements for keeping records of use	
E6	7	Requirements for equipment used to handle substances	
E7	9	Approved handler/security requirements for certain ecotoxic substances	Regulation 9(1) is replaced by: (1) This hazardous substance must be under the personal control of

			an approved handler when the substance is— (a) applied in a wide dispersive manner; or (b) used by a commercial contractor

[36] The regulations can be found on the New Zealand Legislation website; http://www.legislation.co.nz

[37] The term 'passenger service vehicle' is defined in Land Transport Amendment Act 2005

Hazardous Substances (Identification) Regulations 2001

Code	Regulation	Description	Variation
I1	6, 7, 32 – 35, 36(1) – (7)	Identification requirements, duties of persons in charge, accessibility, comprehensibility, clarity and durability	
I3	9	Priority identifiers for ecotoxic substances	
I9	18	Secondary identifiers for all hazardous substances	
I11	20	Secondary identifiers for ecotoxic substances	
I16	25	Secondary identifiers for toxic substances	Revised cut-offs for component labelling required by Regulation 25(e). **HSNO Classification of Component** / **Concentration Cut-off for Label (%)** 6.5A, 6.5B: 0.1[1] 6.6A, 6.7A: 0.1 6.6B, 6.7B: 1 6.7B: 1 6.8A, 6.8C: 0.3 6.8B: 3 6.9A, 6.9B: 10 [1] Identification of sensitising components may be required below the 0.1% level if a lower value has been used for classification.
I17	26	Use of generic names	
I18	27	Requirements for using concentration ranges	
I19	29 – 31	Additional information requirements, including situations where substances are in multiple packaging	
I21	37 – 39, 47 – 50	General documentation requirements	

I23	41	Specific documentation requirements for ecotoxic substances	
I28	46	Specific documentation requirements for toxic substances	
I29	51, 52	Signage requirements	

Hazardous Substances (Packaging) Regulations 2001

Code	Regulation	Description	Variation
P1	5, 6, 7(1), 8	General packaging requirements	
P3	9	Criteria that allow substances to be packaged to a standard not meeting Packing Group I, II or III criteria	
P15	21	Packaging requirements for ecotoxic substances	
PG3	Schedule 3	Packaging requirements equivalent to UN Packing Group III	
PS4	Schedule 4	Packaging requirements as specified in Schedule 4	

Hazardous Substances (Disposal) Regulations 2001

Code	Regulation	Description	Variation
D4	8	Disposal requirements for toxic and corrosive substances	
D5	9	Disposal requirements for ecotoxic substances	
D6	10	Disposal requirements for packages	
D7	11, 12	Information requirements for manufacturers, importers and suppliers, and persons in charge	
D8	13, 14	Documentation requirements for manufacturers, importers and suppliers, and persons in charge	

Hazardous Substances (Emergency Management) Regulations 2001

Code	Regulation	Description	Variation
EM1	6, 7, 9 – 11	Level 1 information requirements for suppliers and persons in charge	
EM6	8(e)	Information requirements for toxic substances	

EM7	8(f)	Information requirements for ecotoxic substances	
EM8	12 – 16, 18 – 20	Level 2 information requirements for suppliers and persons in charge	
EM11	25 – 34	Level 3 emergency management requirements: duties of person in charge, emergency response plans	
EM12	35 – 41	Level 3 emergency management requirements: secondary containment	The following subclauses are adde subclause (3) of regulation 36: *(4) For the purposes of this regula regulations 37 to 40, where thi contained in pipework that is i operated so as to manage any containment in the pipework it-* *(a) is not to be taken into acc determining whether a pla have a secondary contain and* *(b) is not required to be locate secondary containment sy* *(5) In this clause, pipework—* *(a) means piping that—* *(i) is connected to a statio and* *(ii) is used to transfer a ha substance into or out o container; and* *(b) includes a process pipelin line.* The following subclauses are adde regulation 37: *(2) If pooling substances which do 1 to 5 hazard classifications ar above ground in containers ea a capacity of 60 litres or less—* *(a if the place's total pooling than 20,000 litres, the sec containment system must of at least 25% of that tota potential:* *(b) if the place's total pooling 20,000 litres or more, the containment system must of the greater of—* *(i) 5% of the total pooling* *(ii) 5,000 litres.* *(3) Pooling substances to which s applies must be segregated w to ensure that leakage of one*

			not adversely affect the contai substance. The following subclauses are adde regulation 38: *(2) If pooling substances which do 1 to 5 hazard classifications ar above ground in containers 1 c have a capacity of more than 6 of which have a capacity of mo litres—* *(a) if the place's total pooling than 20,000 litres, the sec containment system must of either 25% of that total or 110% of the capacity of container, whichever is the* *(b) if the place's total pooling 20,000 litres or more, the containment system must of the greater of—* *(i) 5% of the total pooling p* *(ii) 5,000 litres* *(3) Pooling substances to which s applies must be segregated w to ensure that the leakage of c may not adversely affect the c another substance.*
EM13	42	Level 3 emergency management requirements: signage	

Hazardous Substances (Tank Wagon and Transportable Containers) Regulations 2004

Code	Regulation	Description
Tank Wagon	4 to 43 as applicable	Controls relating to tank wagons and transportable containers

Schedule 8 of the Hazardous substances (Dangerous Goods and Scheduled Toxic Substances) Transfer Notice 2

Code	Regulation	Description
Sch 8	Schedule 8	This schedule prescribes the controls for stationary container systems. The requirements of t are detailed in the consolidated version of the Hazardous Substances (Dangerous Goods an Toxic Substances) Transfer Notice 2004 available from http://www.epa.govt.nz/Publications/ 35-2004.pdf

Approved Handler

Code	Description
AH1	Approved Handler requirements (including test certificate and qualification requirements). Refer to E7

Additional controls set under Section 77A

Code	Description
Water	This substance shall not be applied onto or into water
App Rate	A maximum application rate is set for this substance. 50 g ai/ha ground based application, maximum three applications per year with minimum application interval of seven days
Label	Additional label information has been specified. The following must be stated on the label: • Use of Benevia must be by ground-based methods[29] • Spray Benevia in flowering crops only after daily honeybee flights, unless the application rate is is less than or equal to 20 gai/ha and spraying after daily honeybee flights is not possible • Ensure flowering weeds are removed before spraying Benevia to avoid potential exposure of honeybees • Ensure spray drift is avoided into flowering off-crop habitats during the application of Benevia

Table 54 Controls for Exirel – codes, regulations and variations

Hazardous Substances (Classes 6, 8, and 9 Controls) Regulations 2001

Code	Regulation	Description	Variation
T1	11 – 27	Limiting exposure to toxic substances through the setting of TELs	No TEL values are set for any components of this substance at this time. The following ADE and PDE values are set for cyantraniliprole: ADE = 0.01 mg/kg bw/day PDE_{Food} = 0.007 mg/kg bw/day PDE_{Water} = 0.002 mg/kg bw/day PDE_{Other} = 0.001 mg/kg bw/day
T2	29, 30	Controlling exposure in places of work through the setting of WESs	The MBIE WES for component G applies to Exirel. http://www.osh.dol.govt.nz/publications/booklets/wes-2013/wes-and-biological-indices-2013.pdf
T4	7	Requirements for equipment used to handle substances	
T5	8	Requirements for protective clothing and equipment	

[29] Ground-based methods of applying pesticides include, but are not limited to, application by ground boom, airblast or knapsack, and do not include aerial application methods

T7	10	Restrictions on the carriage of toxic or corrosive substances on passenger service vehicles[37]	Regulation 10 applies as if the maximum quantity per package of a 6.5B substance is 1.0 L, rather than 0.1 L
E1	32 – 45	Limiting exposure to ecotoxic substances through the setting of EELs	No EEL values are set for this substance at this time and the default EELs are deleted
E2	46 – 48	Restrictions on use of substances in application areas	As no EELs have been set for this substance, no application rate is required to be set. However, a maximum application rate is set under section 77A for this substance
E5	5(2), 6	Requirements for keeping records of use	
E6	7	Requirements for equipment used to handle substances	
E7	9	Approved handler/security requirements for certain ecotoxic substances	Regulation 9(1) is replaced by: (1) This hazardous substance must be under the personal control of an approved handler when the substance is— (a) applied in a wide dispersive manner; or (b) used by a commercial contractor

[36] The regulations can be found on the New Zealand Legislation website; http://www.legislation.co.nz

[37] The term 'passenger service vehicle' is defined in Land Transport Amendment Act 2005

Hazardous Substances (Identification) Regulations 2001

Code	Regulation	Description	Variation
I1	6, 7, 32 – 35, 36(1) – (7)	Identification requirements, duties of persons in charge, accessibility, comprehensibility, clarity and durability	
I3	9	Priority identifiers for ecotoxic substances	
I9	18	Secondary identifiers for all hazardous substances	
I11	20	Secondary identifiers for ecotoxic substances	

<table>
<tr><td>I16</td><td>25</td><td>Secondary identifiers for toxic substances</td><td>Revised cut-offs for component labelling required by Regulation 25(e)

<table><tr><th>HSNO Classification of Component</th><th>Concentration Cut-off for Label (%)</th></tr><tr><td>6.5A, 6.5B</td><td>0.1[1]</td></tr><tr><td>6.6A, 6.7A</td><td>0.1</td></tr><tr><td>6.6B, 6.7B</td><td>1</td></tr><tr><td>6.7B</td><td>1</td></tr><tr><td>6.8A, 6.8C</td><td>0.3</td></tr><tr><td>6.8B</td><td>3</td></tr><tr><td>6.9A, 6.9B</td><td>10</td></tr></table>
[1] Identification of sensitising components may be required below the 0.1% level if a lower value has been used for classification.</td></tr>
<tr><td>I17</td><td>26</td><td>Use of generic names</td><td></td></tr>
<tr><td>I18</td><td>27</td><td>Requirements for using concentration ranges</td><td></td></tr>
<tr><td>I19</td><td>29 – 31</td><td>Additional information requirements, including situations where substances are in multiple packaging</td><td></td></tr>
<tr><td>I21</td><td>37 – 39, 47 – 50</td><td>General documentation requirements</td><td></td></tr>
<tr><td>I23</td><td>41</td><td>Specific documentation requirements for ecotoxic substances</td><td></td></tr>
<tr><td>I28</td><td>46</td><td>Specific documentation requirements for toxic substances</td><td></td></tr>
<tr><td>I29</td><td>51, 52</td><td>Signage requirements</td><td></td></tr>
</table>

Hazardous Substances (Packaging) Regulations 2001

Code	Regulation	Description	Variation
P1	5, 6, 7(1), 8	General packaging requirements	
P3	9	Criteria that allow substances to be packaged to a standard not meeting Packing Group I, II or III criteria	
P13	19	Packaging requirements for toxic substances	
P15	21	Packaging requirements for ecotoxic substances	

PG3	Schedule 3	Packaging requirements equivalent to UN Packing Group III	
PS4	Schedule 4	Packaging requirements as specified in Schedule 4	

Hazardous Substances (Disposal) Regulations 2001

Code	Regulation	Description	Variation
D4	8	Disposal requirements for toxic and corrosive substances	
D5	9	Disposal requirements for ecotoxic substances	
D6	10	Disposal requirements for packages	
D7	11, 12	Information requirements for manufacturers, importers and suppliers, and persons in charge	
D8	13, 14	Documentation requirements for manufacturers, importers and suppliers, and persons in charge	

Hazardous Substances (Emergency Management) Regulations 2001

Code	Regulation	Description	Variation
EM1	6, 7, 9 – 11	Level 1 information requirements for suppliers and persons in charge	
EM6	8(e)	Information requirements for toxic substances	
EM7	8(f)	Information requirements for ecotoxic substances	
EM8	12 – 16, 18 – 20	Level 2 information requirements for suppliers and persons in charge	
EM11	25 – 34	Level 3 emergency management requirements: duties of person in charge, emergency response plans	
EM12	35 – 41	Level 3 emergency management requirements: secondary containment	The following subclauses are adde subclause (3) of regulation 36: *(4) For the purposes of this regula regulations 37 to 40, where thi contained in pipework that is i operated so as to manage any containment in the pipework it-* *(a) is not to be taken into acc determining whether a pla have a secondary contain and*

(b) is not required to be locate
secondary containment sy

(5) In this clause, pipework—

(a) means piping that—

(i) is connected to a statio
and

(ii) is used to transfer a ha
substance into or out o
container; and

(b) includes a process pipelin
line.

The following subclauses are adde
regulation 37:

(2) If pooling substances which do
1 to 5 hazard classifications ar
above ground in containers ea
a capacity of 60 litres or less—

(a if the place's total pooling
than 20,000 litres, the sec
containment system must
of at least 25% of that tota
potential:

(b) if the place's total pooling
20,000 litres or more, the
containment system must
of the greater of—

(i) 5% of the total pooling

(ii) 5,000 litres.

(3) Pooling substances to which s
applies must be segregated w
to ensure that leakage of one
not adversely affect the contai
substance.

The following subclauses are adde
regulation 38:

(2) If pooling substances which do
1 to 5 hazard classifications ar
above ground in containers 1 c
have a capacity of more than 6
of which have a capacity of mo
litres—

(a) if the place's total pooling
than 20,000 litres, the sec
containment system must
of either 25% of that total
or 110% of the capacity of
container, whichever is the

(b) if the place's total pooling
20,000 litres or more, the

			containment system must of the greater of— *(i) 5% of the total pooling p* *(ii) 5,000 litres* *(3) Pooling substances to which s applies must be segregated w to ensure that the leakage of c may not adversely affect the c another substance.*
EM13	42	Level 3 emergency management requirements: signage	

Hazardous Substances (Tank Wagon and Transportable Containers) Regulations 2004

Code	Regulation	Description
Tank Wagon	4 to 43 as applicable	Controls relating to tank wagons and transportable containers

Schedule 8 of the Hazardous substances (Dangerous Goods and Scheduled Toxic Substances) Transfer Notice 2

Code	Regulation	Description
Sch 8	Schedule 8	This schedule prescribes the controls for stationary container systems. The requirements of t are detailed in the consolidated version of the Hazardous Substances (Dangerous Goods an Toxic Substances) Transfer Notice 2004

Approved Handler

Code	Regulation	Description
AH1	Approved Handler requirements (including test certificate and qualification requirements)	

Additional controls set under Section 77A

Code	Description
Water	This substance shall not be applied onto or into water
App Rate	A maximum application rate is set for this substance. 50 g ai/ha ground based application, maximum three applications pe minimum application interval of seven days
Label	Additional label information has been specified. The following must be stated on the label: • Use of Exirel must be by ground-based methods[30]

[30] Ground-based methods of applying pesticides include, but are not limited to, application by ground boom, airblast or knapsack, and do not include aerial application methods

- Spray Exirel in flowering crops only after daily honeybee flights, unless spraying after daily honeybee flights is no
- Ensure flowering weeds are removed before spraying Exirel to avoid potential exposure of honeybees

Appendix D: References

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Appendix E: Confidential Information

Appendix F: Standard terms and abbreviations

ai	active ingredient
ALD50	approximate median lethal dose, 50%
AOEL	acceptable operator exposure level
ARfD	acute reference dose
as	active substance
BCF	bioconcentration factor
bfa	body fluid assay
BOD	biological oxygen demand
BSAF	biota-sediment accumulation factor
bw	body weight
c	centi- ($x10^{-2}$)
CA	controlled atmosphere
CI	confidence interval
CL	confidence limits
CNS	central nervous system
COD	chemical oxygen demand
DFR	dislodgeable foliar residue
DO	dissolved oxygen
DOC	dissolved organic carbon
DT50	period required for 50 percent dissipation (define method of estimation)
DT90	period required for 90 percent dissipation (define method of estimation)
dw	dry weight
ED50	median effective dose
ERC	environmentally relevant concentration

F	field
F0	parental generation
F1	filial generation, first
F2	filial generation, second
fp	freezing point
G	glasshouse
GAP	good agricultural practice
GC	gas chromatography
GC-EC	gas chromatography with electron capture detector
GC-FID	gas chromatography with flame ionization detector
GC-MS	gas chromatography-mass spectrometry
GC-MSD	gas chromatography with mass-selective detection
GLC	gas liquid chromatography
GLP	good laboratory practice
GM	geometric mean
H	Henry's Law constant (calculated as a unitless value) (see also K)
ha	hectare
Hb	haemoglobin
HCG	human chorionic gonadotropin
Hct	haematocrit
HPLC	high pressure liquid chromatography or high performance liquid chromatography
HPLC-MS	high pressure liquid chromatography - mass spectrometry
I	indoor

I50	inhibitory dose, 50%
IC50	median immobilization concentration or median inhibitory concentration 6
ID	ionization detector
Im	intramuscular
inh	inhalation
ip	intraperitoneal
IPM	integrated pest management
iv	intravenous
IVF	in vitro fertilization
K	Kelvin or Henry's Law constant (in atmospheres per cubic meter per mole) (see also H)
Kads	adsorption constant
Kdes	apparent desorption coefficient
Koc	organic carbon adsorption coefficient
Kom	organic matter adsorption coefficient
kg	kilogram
LC	liquid chromatography
LC-MS	liquid chromatography- mass spectrometry
LC50	lethal concentration, median
LCA	life cycle analysis
LC-MS-MS	liquid chromatography with tandem mass spectrometry
LD50	lethal dose, median; dosis letalis media
LDH	lactate dehydrogenase
LOAEC	lowest observable adverse effect concentration
LOAEL	lowest observable adverse effect level
LOD	limit of detection
LOEC	lowest observable effect concentration
LOEL	lowest observable effect level
LOQ	limit of quantification (determination)
LPLC	low pressure liquid chromatography
LSC	liquid scintillation counting or counter
LSS	liquid scintillation spectrometry
LT	lethal threshold
M	molar
µm	micrometer (micron)
MDL	method detection limit
MFO	mixed function oxidase
µg	microgram
MLT	median lethal time
MLD	median lethal dose
mol	Mole(s)
MOS	margin of safety
mp	melting point
MS	mass spectrometry
MSDS	material safety data sheet
NAEL	no adverse effect level
nd	not detected
NEL	no effect level
ng	nanogram
nm	nanometer
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration

NOEL	no observed effect level
NR	not reported
OC	organic carbon content
ODP	ozone-depleting potential
OM	organic matter content
Pa	pascal
PEC	predicted environmental concentration
PECS	predicted environmental concentration in soil
PECSW	predicted environmental concentration in surface water
PECGW	predicted environmental concentration in ground water
PHI	pre-harvest interval
pKa	negative logarithm (to the base 10) of the dissociation constant)
PNEC	predicted no effect concentration
POW	partition coefficient between n-octanol and water
ppb	parts per billion (10^{-9})
PPE	personal protective equipment
ppm	parts per million (10^{-6})
ppp	plant protection product
ppq	parts per quadrillion (10^{-24})
ppt	parts per trillion (10^{-12})
PTDI	provisional tolerable daily intake
r	correlation coefficient
r2	coefficient of determination
REI	restricted entry interval
Rf	retardation factor
RfD	reference dose
RL50	median residual lifetime
RP	reversed phase
RRT	relative retention time
RSD	relative standard deviation
sc	subcutaneous
SD	standard deviation
se	standard error
SF	safety factor
SIMS	secondary ion mass spectroscopy
SOP	standard operating procedures
sp	species (only after a generic name)
SPE	solid phase extraction
spp	subspecies
SSD	sulphur specific detector
STEL	short term exposure limit
t½	half-life (define method of estimation)
TCLo	toxic concentration, low
TER	toxicity exposure ratio
TIFF	tag image file format
TOC	total organic carbon
TWA	time weighted average
UF	uncertainty factor (safety factor)
ULV	ultra low volume
UV	ultraviolet
v/v	volume ratio (volume per volume)
w/v	weight per volume
ww	wet weight
w/w	weight per weight