ERMA New Zealand
Evaluation and Review Report

Application for Approval to Import Vivando for Release

Application Number: HSR08113

Prepared for the Environmental Risk Management Authority

EXECUTIVE SUMMARY

Background information

- BASF New Zealand Limited is seeking approval to import Vivando for release.
- Vivando is a fungicide containing metrafenone in the form of a suspension concentrate.
- Vivando is proposed to be used as a systemic fungicide for the control of powdery mildew in pumpkin and winter squash.
- Vivando will be applied as a fungicide at a maximum application rate of 154.5 g a.i./ha., twice per season, with a minimum application interval of 14 days.
- Metrafenone is a new active ingredient to New Zealand.

Key issues

- The Agency has classified Vivando based on the composition of Vivando and the effects of its components. The Agency's classifications are different from the applicant's proposed HSNO classifications (Table 1).

Table 1: Summary of the applicant's and Agency's classifications of Vivando

Hazardous Property	Applicant's Assessment	Agency's Assessment
Carcinogenicity	-	6.7B
Aquatic Ecotoxicity	9.1B	9.1D (Biocide)

- The Agency's classifications differ from the applicant's due to aquatic ecotoxicity classifications generated from formulation test data (Agency) or mixture rules (applicant).
- The Agency assigned a 6.7B "suspected human carcinogen" classification to Vivando, based on the assignment of this classification to the active ingredient. The Agency used a weight of evidence approach in reaching this conclusion taking into account the increase in incidence of benign liver tumours in rats and benign and malignant liver tumours in mice. The Agency also took into account supplementary studies on mode of action.
- The Agency notes that this conclusion is consistent with the US EPA data summary conclusion: "Suggestive evidence of carcinogenicity".
- The Agency also notes that, based on information available, a human carcinogenicity risk would only occur after prolonged exposure at high levels.
- The applicant was provided with a copy of the draft E&R report including the proposed controls. The applicant commented on the carcinogenicity classification (6.7B) and provided additional information. Following a review of this information and discussions with the applicant, the Agency concluded it is appropriate to retain the 6.7B classification for Vivando.

- The Agency used the operator exposure modeling to estimate exposure to metrafenone from the use of Vivando. The exposure estimates were compared to the Acceptable Operator Exposure Level of 0.43 mg/kg bw/day. The operator risks were estimated to be acceptable even if no personal protective equipment is worn by the operator, so the human health risks to operator, flaggers/re-entry workers, and bystanders are considered to be negligible.

- The Agency proposes the establishment of an ADE for metrafenone to enable the setting of a PDE_{food}, which may be needed by the New Zealand Food Safety Authority for the setting of MRLs. Therefore the Agency proposes an **ADE for metrafenone of 0.25 mg/kg bw/day**, a **PDE_{food} of 0.18 mg/kg bw/day** and a **PDE_{water} of 0.05 mg/kg bw/day**. The Agency does not propose the setting of an acute reference dose (ARfd) due to the low acute toxicity of metrafenone.

- The Agency does not propose the setting of any Tolerable Exposure Limits (TELs) or Workplace Exposure Standards (WES) for components of Vivando at this time.

- Metrafenone exhibited high persistence in soil under aerobic conditions, with field and laboratory half lives exceeding 100 days. Based on the sorption studies metrafenone is not expected to be mobile in soil, therefore no leaching studies were submitted. Field studies have shown that metrafenone is expected to accumulate in soil with continuous use. A plateau is expected to be reached after 6 – 10 years use.

- Despite its non-rapid degradation in water and high persistence and accumulative potential in soil, the results of ecotoxicity testing of both the active ingredient and the formulation has shown no deleterious effects to standard test species, including beneficial insects. However, as with all environmentally persistent chemistry, some uncertainty exists.

- Although no EEL has been set for Vivando, the Agency proposes setting the application rate of 154.5 g ai/ha (0.3 L formulation/ha), twice per season as the maximum application rate for Vivando. This rate was used in the ecological risk assessment.

- Controls applicable to a 9.1D (biocide) substance are to be applied.

Key issues from current reviews

- The Agency notes that metrafenone and products containing metrafenone have been recently reviewed by EFSA, 2006. This report has highlighted the following concerns:

    - The risk to birds and mammals from secondary poisoning is regarded to be low for the representative uses evaluated. The risk to birds and mammals from consumption of contaminated drinking water is considered to be low except for the long term risk to birds in cereals for which the Toxicity Exposure Ratio (TER) value is below the trigger value indicating a high long term risk to birds in cereals from drinking contaminated drinking water. Therefore, EFSA proposes a data requirement for the notifier to refine the long term risk to birds in cereals from exposure to contaminated drinking water.

Controls to be applied under Section 77A of the Act

- Vivando is not to be applied into/onto water.
- The maximum application rate for Vivando shall be 154.5 g a.i./ha., twice per season.

TABLE OF CONTENTS

1 APPLICATION DETAILS

Application Code	HSR08113
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")
Applicant	BASF New Zealand Limited
Date Application Received	16 October 2008
Submission Period	31 October 2008 – 12 December 2008
To be considered by	A Committee of the Authority ('the Committee")
Purpose of the Application	To import or manufacture the fungicide VIVANDO for use as a dilute foliar spray to control powdery mildew on commercial cucurbit crops.

2 LEGISLATIVE CRITERIA FOR THE APPLICATION

2.1 The application was lodged pursuant to section 28.

2.2 This report takes into account matters to be considered in section 29; matters specified under Part 2 of the Act; and the relevant provisions of the Hazardous Substances and New Organisms (Methodology) Order 1998 ("the Methodology"). Unless otherwise stated, references to section numbers in this report refer to sections of the Act and clauses to clauses of the Methodology.

3 APPLICATION PROCESS

3.1 Evaluation of the application was undertaken by the ERMA New Zealand project team ("the Agency") which comprised the following staff members:

Jo Prankerd	Advisor (Hazardous Substances)
Jim Waters	Senior Advisor (Hazardous Substances)
Eugene Georgiades	Advisor (Hazardous Substances)
Patrick Gemmell	Advisor (Māori Unit).

3.2 The report was reviewed and signed out by:

Noel McCardle	Senior Advisor (Hazardous Substances)

3.3 Timeline

Application formally received	16 October 2008
Application notified	31 October 2008
Submission closing date	12 December 2008.

3.4 Further information was requested from the applicant during the evaluation and review of this application in accordance with section 58 and consequently the consideration was postponed for 13 working days.

3.5 Due to delays in completing this E&R Report, the Authority postponed the consideration under section 58(3) until 11 August 2009.

4 NOTIFICATION AND CONSULTATION

4.1 The Minister for the Environment was advised of the application[1] and given the opportunity to "call-in" the application[2]. This action was not initiated.

4.2 The Department of Labour (Workplace Group), the New Zealand Food Safety Authority (Agricultural Compounds and Veterinary Medicines (ACVM) Group) and the Department of Conservation were identified as having a specific interest in the application and were provided with a copy of the application (excluding the confidential information but with the opportunity to access this if necessary).

4.2.1 No comments or submissions were received.

4.3 Other Government departments, Crown agencies and other interested parties, as listed in Appendix 7, were provided with a copy of the application summary and given the opportunity to comment or to make a submission.

4.3.1 No comments or submissions were received.

4.4 The application was publicly notified on the ERMA New Zealand website on 31 October 2008 and subsequently advertised in The Dominion Post, the New Zealand Herald, the Christchurch Press and the Otago Daily Times[3].

4.4.1 No submissions were received.

[1] section 53(4)(a))

[2] section 68

[3] section 53

5 APPLICATION SYNOPSIS AND INFORMATION REVIEW

Information supplied by the applicant

5.1 The applicant supplied the following documents:

- the application;
- a confidential appendix (including full formulation data and a draft label).

Information review

5.2 The confidential information on the composition of Vivando has been withheld at the request of the applicant for reasons of commercial sensitivity. The information is provided for the Committee in Confidential Appendix 8.

5.3 The Agency considers that there are no significant uncertainties sufficient to influence decision making in the scientific and technical information relating to the potential adverse effects of Vivando[4]. Therefore, the Agency considers that the information constitutes an adequate and appropriate basis for considering the application[5].

Description and use of the substance

5.4 Vivando is a fungicide containing metrafenone in the form of a suspension concentrate. Vivando is proposed for use as a systemic fungicide for the control of powdery mildew in pumpkin and winter squash.

Lifecycle

Manufacture/Importation

5.5 The applicant has indicated that Vivando will be imported into New Zealand pre-packed.

5.6 While Vivando will be manufactured overseas, it is possible that the substance could be manufactured in New Zealand in the future. Consequently, the risks associated with the manufacture of Vivando have been evaluated, so that approval of this substance will be applicable to both the import and manufacture of Vivando. The Agency notes that in order to manufacture Vivando in New Zealand, a separate approval to import or manufacture metrafenone in New Zealand is required.

Transport, storage and packaging

5.7 Vivando will be packaged according to the requirements of the Hazardous Substances (Packaging) Regulations 2001. The applicant has indicated that pre-packing will minimise handling of the substance in New Zealand and the small individual units will minimise any exposure that might result from an accident.

[4] clauses 29 and 30

[5] clause 8

5.8 The applicant has indicated that both transportation and storage of Vivando will be consistent with the controls associated with a substance with these classifications.

Use

5.9 Vivando is intended for use as a dilute foliar spray to control powdery mildew on commercial pumpkin and winter squash crops. Vivando will be applied at a maximum application rate of 154.5 g a.i./ha (0.3 L formulation/ha) twice per season.

Disposal

5.10 The applicant has advised that the normal method of disposal will be via use. The applicant indicated possible disposal routes including application to an unsprayed portion of the crop, storage and subsequent transport to an approved waste disposal site, treatment on the farm using suitable equipment designed to treat liquid waste containing pesticides and application to an uncropped area of land of minimal wildlife value. The applicant recommends that all attempts should be made to use this product completely in accordance with its registered use to avoid disposal.

5.11 The applicant further notes that empty containers may retain some product residues and both the container and rinsate be disposed of in a safe manner.

5.12 In all cases the substance and its packaging will be disposed of in accordance with the Hazardous Substances (Disposal) Regulations 2001 and the Resource Management Act 1991.

6 HAZARDOUS PROPERTIES, THRESHOLDS AND CLASSIFICATION

6.1 The Agency has evaluated the information supplied by the applicant and also referred to other data sources in assessing the hazardous properties of Vivando. This assessment is attached as Appendix 2.

6.2 The applicant's and the Agency's classification of the hazard profiles of Vivando are listed in Table 6.1.

Table 6.1: Summary of applicant's and Agency's HSNO classification of Vivando

Hazardous Property	Applicant's Assessment	Agency's Assessment
Carcinogenicity	-	6.7B
Aquatic Ecotoxicity	9.1B	9.1D (Biocide)

6.3 The Agency assigned a 6.7B "suspected human carcinogen" classification to Vivando, based on the assignment of this classification to the active ingredient. The Agency used a weight of evidence approach in reaching this conclusion taking into account the increase in incidence of benign liver tumours in rats and benign and malignant liver tumours in mice. The Agency also took into account supplementary studies on mode of action.

6.4 The Agency notes that this conclusion is consistent with the US EPA data summary conclusion: "Suggestive evidence of carcinogenicity" but notes that based on information available, if there is a human carcinogenicity risk, it would only occur after prolonged high exposure levels.

6.5 The Agency's classification differs to that of the applicant's for 9.1 as the Agency considers that, based on the available data, Vivando does not trigger the threshold for toxicity in the aquatic environment, other than as a 9.1D biocide.

6.6 The risk assessment in Section 8 of this report is based on the Agency's classification of Vivando.

7 DEFAULT CONTROLS

7.1 Based on the hazard classifications as shown in Table 6.1, the set of associated default controls have been identified. These default controls are listed in Appendix 4.

7.2 The Authority is able to vary the default controls and impose controls under sections 77 and 77A to produce a set of controls relevant to Vivando. Variations and additional controls for Vivando are considered in Section 10 of this report.

8 RISK ASSESSMENT

Identification of potentially non-negligible risks and costs

8.1 Potentially non-negligible risks were identified for evaluation following clauses 9 and 11, which incorporate sections 5, 6 and 8.

8.2 A "cost" is defined in Regulation 2 of the Methodology as "the value of a particular adverse effect expressed in monetary or non-monetary terms". Thus, these have been assessed in an integrated fashion together with the risks of the adverse effects in the following assessment.

8.3 The applicant has identified potential sources of risk to the environment and to human health and safety through release, spillage or exposure throughout the lifecycle of the substance. The Agency has also identified potential sources of risk and these, along with those identified by the applicant, are tabulated in Table 8.1.

Table 8.1: Potential sources of risks associated with Vivando

Lifecycle Activity	Associated Source of Risk
Manufacture / Import	An incident during the manufacture or importation of Vivando, resulting in spillage and subsequent exposure of people or the environment to the substance.
Packing	An incident during the packing of Vivando 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 Vivando resulting in spillage and subsequent exposure of people or the environment to the substance.

Lifecycle Activity	Associated Source of Risk
Use	Application of Vivando 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 Vivando or packaging resulting in exposure of people or the environment to the substance.

Assessment of potentially significant risks

8.4 In accordance with sections 5 and 6 and clauses 9 and 12, the Agency has assessed the potentially non-negligible risks of this substance in terms of risks to the environment, to human health and safety, to the relationship of Māori to the environment, to society and the community, to the market economy, and to New Zealand's international obligations.

8.5 The Agency notes that the evidence provided by the applicant and additional evidence found by the Agency, relating to the hazardous properties of Vivando, is largely scientific in nature[6]. However, as some of the evaluation of risks, costs and benefits has been carried out on a qualitative basis, it is recognised that there is a degree of uncertainty in the risk analysis.

8.6 The analysis of risk takes into account the controls that derive from the HSNO Regulations (in particular the default controls identified in Appendix 4) and from other legislation such as the Resource Management Act 1991 and the Health and Safety in Employment Act 1992. That is, the analysis assumes controls are in place.

8.7 A quantitative risk assessment has been carried out to evaluate the level of risk to operators and the environment arising from the use of Vivando (see Appendix 3).

8.8 A qualitative assessment has 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 (see Appendix 3).

Assessment of the risks to the environment

8.9 The Agency has classified Vivando as being designed for biocidal action (9.1D).

8.10 The Agency considers that the likelihood of exposure to the environment is greatest during use of the substance.

8.11 The quantitative assessment of the risks to the aquatic environment associated with the use of Vivando has not identified any risks to any of the species examined (see Appendix 3).

[6] clause 25(1)

8.12 No acute risk assessment was performed as no acute effects have been demonstrated (see Appendix 3).

8.13 The Agency considers that application of the following controls are necessary in order for the risks to the environment from the use of substance to remain low:

- Prohibiting the application of Vivando into or onto water;
- Setting of a maximum application rate and maximum application frequency.

8.14 The risks of Vivando to the environment (with controls in place) at various stages of its lifecycle are summarised below in Table 8.2 and discussed more fully in Appendix 3.

Table 8.2: Level of risk of Vivando to the environment.

Lifecycle Stage	Potential Adverse Effect	Likelihood of Adverse Effect Occurring	Magnitude of Adverse Effect	Level of Risk
Manufacture, importation, transport and storage	Spillage resulting in death or adverse effects to aquatic or terrestrial organisms in the environment.	Highly improbable	Minor	Negligible
Use	Use resulting in death or adverse effects to aquatic organisms in the environment.	Quantitative assessment indicated that the chronic risk to fish and crustacea in the aquatic environment is low during use. A quantitative acute risk assessment was not performed as no acute effects have been demonstrated.		
Disposal	Disposal resulting in death or adverse effects to aquatic or terrestrial organisms in the environment.	Highly improbable	Minor	Negligible

Assessment of the risks to human health and safety

8.15 The Agency has classified Vivando as a suspected carcinogen (6.7B).

8.16 In the Agency's opinion, chronic hazards, such as carcinogenicity, normally require repeated exposure to the substance for the adverse effects to occur and are therefore most relevant to the end-users.

8.17 The Agency assessed the health risk to operators on the basis of the German BBA model predictions for exposure estimates. The quantitative modelling indicates that, at the highest application rates, the exposure to Vivando, when used as recommended on the label, is not likely to present a high health risk to the mixers or applicators, even without the use of basic protective clothing, such as gloves.

8.18 The Agency notes that the requirement for personal protective equipment (PPE) is triggered as a default control for Vivando as a result of its 6.7B classification. Even though the 'no PPE' exposure model leads to an acceptable level of risk, the Agency considers that it is appropriate to retain requirements for PPE, since the use

of PPE when handling agrichemicals is good practice. The Agency, therefore, concludes that the health risk to operators, with controls in place, is ***negligible***.

8.19 The main potential source of exposure to the general public from Vivando is via spray drift. The results from the quantitative modelling of operator exposure indicate the risk to operators from Vivando is low even if PPE is not worn. The Agency notes that although any potential bystanders will not be wearing PPE, they will not be directly handling the substance. The Agency concludes the risk to bystanders from the use of Vivando to be ***negligible***.

8.20 The risks of Vivando to human health and safety (with controls in place) at various stages of the lifecycle are summarised below in Table 8.3 and discussed more fully in Appendix 3.

Table 8.3: Level of risk of Vivando to human health and safety.

Lifecycle stage	Potential Adverse Effect	Likelihood of Adverse Effect Occurring	Magnitude of Adverse Effect	Level of Risk
Manufacture/ packing	Carcinogenicity	Quantitative assessment indicates that the chronic risks to human health and safety during use are acceptable even without the use of PPE. The Agency considers workers involved in the manufacture of Vivando will be required to comply with the requirements for PPE and considers the level of risk during manufacture and packing to be negligible.		
Importation, transport or storage	Carcinogenicity	Not addressed		
Use	Chronic effects: operators (quantitative assessment)			
	Carcinogenicity	Quantitative assessment indicated that the chronic risks to human health and safety are acceptable even without the use of PPE and the level of risk is considered to be negligible.		
	Chronic effects: bystanders (quantitative assessment)			
	Carcinogenicity	Quantitative assessment indicated that the chronic risks to bystander human health and safety are acceptable and the level of risk is considered to be negligible.		
Disposal	Carcinogenicity	Highly improbable	Minor	Negligible

Relationship of Māori to the Environment

8.21 The Agency has considered this application in accordance with the clauses 9(b)(i) and 9(c)(iv) and sections 6(d) and 8. In addition, the framework contained in the ERMA New Zealand user guide "Working with Māori under the HSNO Act 1996" has been used to assess the effects of this application on the relationship of Māori to the environment.

8.22 The Agency notes that Vivando triggers a number of hazardous properties giving rise to the potential for cultural risk including the deterioration of the mauri of taonga flora and fauna species, the environment and the general health and well-being of individuals and the community.

8.23 In addition, the introduction and use of this substance has the potential to inhibit the ability of iwi/Māori to fulfil their role as kaitiaki, particularly in relation to the guardianship of waterways given the highly ecotoxic nature of the substance to aquatic species, and potential risks to the mauri ora of human health under prolonged exposure to this substance.

8.24 On considering the information outlined here and elsewhere in this report, the Agency considers a ***minimal*** impact from Vivando on the relationship of Māori and their culture and traditions with their ancestral lands, water, sites, wāhi tapu, valued flora and fauna and other taonga to be ***highly improbable***. In addition there is no evidence to suggest that the controlled use of Vivando will breach the principles of the Treaty of Waitangi.

8.25 The overall level of risk is therefore considered to be ***negligible*** assuming that the substance will be handled, stored, transported, used, and disposed of, in accordance with the explicitly stated default and additional controls proposed in this report, and any other controls required by other legislation.

8.26 However, the Agency notes that should inappropriate use, or accident, result in the contamination of waterways or the environment generally, that users notify the appropriate authorities including the relevant iwi authorities in that region. This action should include advising them of the contamination and the measures taken to contain and remediate.

Assessment of the risks to society and the community

8.27 There are not expected to be any significant adverse impacts on the social environment with the controlled use of Vivando, apart from the health effects and environmental effects already discussed. Consequently, the Agency considers that this aspect of potential risk need not be considered further.

Assessment of the risks to the market economy

8.28 Taking into account the level of risk to the environment and to human welfare, no sources of additional risk have been identified that could result in an adverse economic impact on a community.

8.29 The Agency notes that direct economic costs will be borne by the applicant and users of the substance. The HSNO default controls intentionally do not manage direct economic effects. These are for suppliers and users of the substance to address.

New Zealand's international obligations

8.30 The Agency does not anticipate that Vivando will pose any risks to New Zealand's international obligations.

9 ASSESSMENT OF BENEFICIAL EFFECTS

Potentially non-negligible benefits

9.1 A "benefit" is defined in Regulation 2 of the Methodology as "the value of a particular positive effect expressed in monetary or non-monetary terms". Benefits that may arise from any of the matters set out in clauses 9 and 11 were considered in terms of clause 13.

9.2 The applicant notes Vivando offers significant benefits to the end-user as powdery mildew is the major disease in cucurbit crops, particularly in the production of export squash.

9.3 The applicant indicates that the effectiveness of current chemistry in controlling powdery mildew is rapidly diminishing due to the development of resistant strains of the fungus. As such, the applicant considers Vivando to be the most active product against this disease and with its new mode of action Vivando will provide the grower with a needed tool to enable the continued production of quality squash for export.

9.4 The Agency considers that the economic and related benefits to be derived from the use of Vivando are potentially significant.

Likely effects of the substance being unavailable

9.5 In accordance with section 29, consideration has been given to the likely effects of Vivando being unavailable.

9.6 The Agency notes that there are no products currently available in New Zealand containing metrafenone. The likely effects of Vivando being unavailable would thus be a reduction in consumer choice for end-users, as a result of the reduction in the variety of active ingredients for the control of powdery mildew.

Risk reduction implications

9.7 The applicant has not provided information on any significant risk reduction implications for the import or manufacture of Vivando for release.

9.8 The Agency notes that the toxicity profile for Vivando is relatively low in comparison to other approved substances used for various fungal diseases.

10 CONTROLS

Setting of exposure limits and application rates

10.1 Control **T1** relates to the requirement to limit public exposure to toxic substances by the setting of Tolerable Exposure Limits (TELs). The Agency proposes the setting of the following exposure limits for metrafenone:

- ADE = 0.25 mg/kg bw/day;
- PDE_{food} = 0.18 mg/kg bw/day;

- PDE_{water} = 0.05 mg/kg bw/day.

The Agency is not proposing that any TEL values be set for Vivando until implementation of a pending review of setting such values under section 77B (see Appendix 4). Furthermore, the Agency does not propose that an acute reference dose (ARfD) be set in New Zealand due to the low toxicity of the compound (see Appendix 4).

10.2 Control **T2** relates to the requirement to limit worker exposure to toxic substances by the setting of Workplace Exposure Standards (WESs). No WESs are proposed for any components of Vivando at this time (see Appendix 4).

10.3 Control **E1** relates to the requirements to limit exposure of non-target organisms in the environment through the setting of Environmental Exposure Limits (EELs). It is proposed that **no EELs** are set at this time for Vivando and the default values are **deleted** (see Appendix 4)**.**

10.4 Control **E2** relates to the requirement to set an application rate for a class 9 substance that is to be sprayed on an area of land (or air or water) and for which an EEL has been set. Although no EEL has been set for Vivando, the Agency proposes to set an application rate under section 77A (see paragraph 10.5.1). This application rate was used in the ecological risk assessment.

Proposed additions and modifications to controls

10.5 As a result of the quantitative risk assessment, the Agency considers that in order for the risks to the environment from the use of this substance to remain low, it is appropriate to set the application rate used in the modelling as the maximum application rate and to prohibit the application of Vivando to water (refer Appendix 4). Accordingly, the following additional controls are proposed for Vivando as being more effective than the specified (default) controls in terms of their effect on the management, use and risks of the substance (section 77A(4)(a)):

10.5.1 *"The maximum application rate for Vivando shall be 154.5 g ai/ha (0.3 L formulation/ha), twice per season."*

10.5.2 *"Vivando shall not be applied onto or into water."*

10.5.3 The controls relating to stationary container systems, as set out in Schedule 8 of the Hazardous Substances (Dangerous Goods and Scheduled Toxic Substances) Transfer Notice 2004 (Supplement to the New Zealand Gazette, 26 March 2004, No. 35, page 767), as amended, are proposed for this substance, notwithstanding clause 1(1) of that schedule.

10.5.4 The Agency considers that the following subclauses should be added after subclause (3) of regulation 36 of the Hazardous Substances (Emergency Management) Regulations 2001[7]:

[7] These sub-clauses were applied to pesticides on transfer to the Act.

(*4*) *For the purposes of this regulation, and regulations 37 to 40, where this substance is contained in pipework that is installed and operated so as to manage any loss of containment in the pipework it—*

(a) is not to be taken into account in determining whether a place is required to have a secondary containment system; and

(b) is not required to be located in a secondary containment system.

(5) In this clause, pipework—

(a) means piping that—

(i) is connected to a stationary container; and

(ii) is used to transfer a hazardous substance into or out of the stationary container; and

(b) includes a process pipeline or a transfer line.

10.5.5 The following subclauses should be added after subclause (1) of regulation 37 of the Hazardous Substances (Emergency Management) Regulations 2001:

(2) If pooling substances that do not have class 1 to 5 hazard classifications are held in a place above ground in containers each of which has a capacity of 60 litres or less—

(a) if the place's total pooling potential is less than 20,000 litres, the secondary containment system must have a capacity of at least 25% of that total pooling potential:

(b) if the place's total pooling potential is 20,000 litres or more, the secondary containment system must have a capacity of the greater of—

(i) 5% of the total pooling potential; or

(ii) 5,000 litres.

(3) Pooling substances to which subclause (2) applies must be segregated where appropriate to ensure that leakage of one substance may not adversely affect the container of another substance.

10.5.6 The following subclauses should be added after subclause (1) of regulation 38 of the Hazardous Substances (Emergency Management) Regulations 2001:

(2) If pooling substances which do not have class 1 to 5 hazard classifications are held in a place above ground in containers 1 or more of which have a capacity of more than 60 litres but none of which have a capacity of more than 450 litres—

(a) if the place's total pooling potential is less than 20,000 litres, the secondary containment system must have a capacity of either 25% of that total pooling potential or 110% of the capacity of the largest container, whichever is the greater:

(b) if the place's total pooling potential is 20,000 litres or more, the secondary containment system must have a capacity of the greater of—

(i) 5% of the total pooling potential; or

(ii) 5,000 litres

(3) Pooling substances to which subclause (2) applies must be segregated where appropriate to ensure that the leakage of one substance may not adversely affect the container of another substance.

10.6 The Agency considers that the following controls may be **combined** under section 77(5) for Vivando as they relate to the same requirements:

10.6.1 Controls **T4** and **E6** which relate to requirements for equipment used to handle Vivando.

10.6.2 Controls **D4** and **D5** which relate to requirements for disposal of Vivando.

Control precedents

10.7 The Agency considered the Authority's approvals given to pesticides under Part 5 of the Act as well as those transferred to the Act under the *Hazardous Substances (Pesticides) Transfer Notice 2004 (as amended)*.

Summary of controls

10.8 The Agency considers that the customised controls listed in Appendix 5 should apply to Vivando.

Environmental user charges

10.9 Section 96 provides that the Authority may identify and report to the Minister where it considers that a reduction in the likely occurrence of adverse effects similar to that achieved by the controls attached to any substance could be achieved by any environmental user charge, or a combination of an environmental user charge and controls.

10.10 The Agency considers that use of controls is the most effective means of managing the risks throughout the lifecycle of Vivando. The imposition of an environmental user charge instead of, or in combination with controls, is therefore not required at this time.

11 OVERALL EVALUATION OF RISKS, COSTS AND BENEFITS

11.1 The Agency considers the risks of Vivando to human health and the environment to be ***negligible.***

11.2 The Agency does not consider there to be significant risks to Māori cultural wellbeing, society and the community, the market economy, or to New Zealand's international obligations.

11.3 The Agency has taken the type and severity of the risks, and the characteristics of such risks into account, and considers that the overall level of risk posed by the substance is ***negligible***.

11.4 The Agency considers that there are ***significant*** benefits associated with the release of Vivando as are specified in Section 9 of this report.

11.5 Thus, the Agency considers that it is evident that the benefits of releasing Vivando outweigh the costs.

12 CONCLUSION

12.1 BASF New Zealand Limited has applied for approval to import or manufacture for release in New Zealand the substance identified as Vivando.

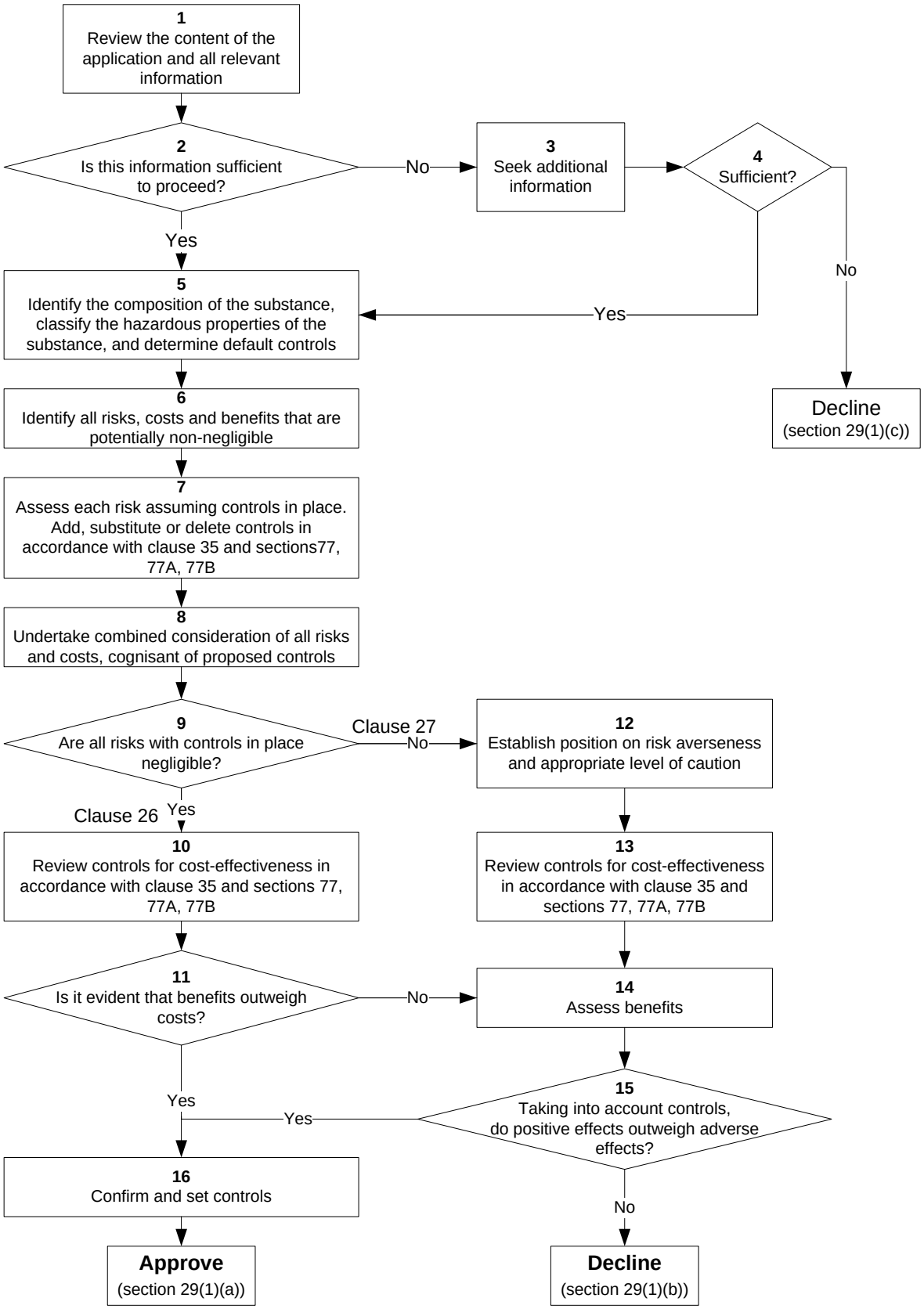
12.2 The Agency considers Vivando triggers the following hazard classifications:

- 6.7B Carcinogenicity
- 9.1D Aquatic ecotoxicity.

12.3 The Agency considers that there are negligible risks to the environment and human health and significant benefits associated with the release of Vivando. Therefore, the Agency considers that it is evident that the benefits of releasing Vivando outweigh the costs and the application may be approved in accordance with clause 26.

12.4 The Agency considers the controls listed in Appendix 5 should apply to Vivando.

APPENDIX 1: DECISION PATH



APPENDIX 2: HAZARD CLASSIFICATION

Classification of Vivando

Formulation data were not provided for all endpoints of Vivando. For endpoints for which formulation data were not provided, classification was estimated using mixture rules based on information on the components. Details of the key substance components and the methods used to derive the classifications are presented in Table A2.1. The relevant sections of the User Guide to the Thresholds and Classifications in the HSNO Act (ERMA 2008a) that describes the mixture rules are listed in Table A2.2.

The active ingredient, metrafenone, is a new pesticide active ingredient to New Zealand. The Agency has provided a summary of the toxicity, ecotoxicity and environmental fate data for metrafenone in Tables A2.5 to A2.12a.

Data quality – overall evaluation

The Agency has adopted the Klimisch et al (2001) data reliability scoring system for evaluating data used in the hazard classification and risk assessment of metrafenone and Vivando (Section 1.2.4 in ERMA 2008a). Scores for individual studies, as evaluated by the Agency, are included in the data assessment tables A2.5 to A2.12. Overall, data provided for metrafenone and Vivando were of high quality [Klimisch scores 1 or 2]. Data on components of Vivando were generally of lower quality [Klimisch scores 3 or 4]. However, the effect of the lower quality data on the overall evaluation of the effects of Vivando was not significant given the quality of the formulation data supplied by the applicant.

The Agency acknowledges 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 (OECD 1990) and REACH (EU 2006) are progressively working towards filling these data gaps. As new information becomes available, and resources permit, the Agency will endeavour to update the HSNO classifications for those substances.

References

ERMA New Zealand 2008a. *User Guide to HSNO Thresholds and Classifications.* ERMA New Zealand, Wellington.

European Union 2006. *Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC*. http://reach.jrc.it/

Klimisch, HJ, Andreae, E, Tillman, U 1997. A systematic approach for evaluating the quality of experimental and ecotoxicological data. *Regulatory Toxicology and Pharmacology* 25: 1–5.

OECD 1990. Manual for Investigation of HPV Chemicals. http://www.oecd.org/document/21/0,3343,en_2649_34379_1939669_1_1_1_1,00.html Retrieved 23 January 2008.

Table A2.0: Physical and chemical properties of Vivando.

Test	Vivando	Method	Reference
Appearance	Beige, homogeneous viscous liquid with < 1% v/v supernatant layer	RLA 11803	Baker, 2001 Study no. FR013/D GLP Klimisch score: 1
Odour	Storage: 52 weeks at 20°C: Aliphatic odour 52 weeks at 25°C: Aliphatic odour 52 weeks at 28°C: Aliphatic odour	RLA 12647	Baker, 2002 Study no. FR013/D GLP Klimisch score: 1
Density at 20°C	1.19 g/mL	CIPAC MT 3.3.1	Baker, 2001 Study no. FR013/D GLP Klimisch score: 1
Surface tension at 25°C	Neat product: 41.1 mN/m 0.013% v/v dilution: 62.4 mN/m	EC a5	
pH	Neat: 8.7 1% dilution: 7.2	CIPAC MT 75.1 (neat) CIPAC MT 75.1 (1% dilution)	
Flash point	Does not contain any substances classified as extremely flammable, highly flammable or flammable.	ERMA NZ assessment	
Auto flammability	Does not contain any substances classified as extremely flammable, highly flammable or flammable.	ERMA NZ assessment	
Explosive properties	Does not contain any substances classified as explosive. No evidence of explosive properties, test EC A14 not required.	ERMA NZ assessment	
Oxidising properties	Does not contain any substances classified as oxidising. No evidence of oxidising properties, test EC A17 not required.	ERMA NZ assessment	

Table A2.1: Summary of the toxicology and ecotoxicology hazard classifications of Vivando.

Hazardous Property	Agency Classification	Classification Method	Component(s) driving classification
6.1 Oral	No	Formulation data	N/A
6.1 Dermal	No	Formulation data	N/A
6.1 Inhalation	No	Formulation data	N/A
6.3/8.2 Skin irritation/corrosion	No	Formulation data	N/A
6.4/8.2 Eye irritation/corrosion	No	Formulation data	N/A
6.5 Respiratory sensitization	No	Mixture rules	None
6.5 Contact sensitisation	No	Formulation data	N/A
6.6 Mutagenicity	No	Mixture rules	None
6.7 Carcinogenicity	6.7B	Mixture rules	6.7B
6.8 Reproductive developmental toxicity	No	Mixture rules	None
6.9 Target organ systemic toxicity	No	Mixture rules	None
9.1 Aquatic ecotoxicity	9.1D	Formulation data	Biocide
Aquatic Persistence	Yes	Active ingredient data	Metrafenone
Bioaccumulative	No	Active ingredient data	Metrafenone
9.2 Soil ecotoxicity	No	Formulation data	N/A
Soil Persistence	Yes	Active ingredient data	Metrafenone
9.3 Terrestrial vertebrate ecotoxicity	No	Formulation data	N/A
9.4 Terrestrial invertebrate ecotoxicity	No	Formulation data	N/A

Table A2.2: Location of mixture rules within the HSNO Thresholds and Classifications User Guide (V2.0. March 2008).

Hazard	User Guide to HSNO Thresholds and Classifications Reference
Subclass 6.1 Acute Toxicity	Part V, Chapter 10, Page 12
Subclass 6.3/8.2 Skin Irritancy/Corrosivity	Part V, Chapter 11, Page 7
Subclass 6.4/8.3 Eye Irritancy/Corrosivity	Part V, Chapter 12, Page 9
Subclass 6.5 Contact and Respiratory Sensitisation	Part V, Chapter 13, Page 8
Subclass 6.6 Mutagenicity	Part V, Chapter 14, Page 5
Subclass 6.7 Carcinogenicity	Part V, Chapter 15, Page 8
Subclass 6.8 Reproductive Developmental Toxicity	Part V, Chapter 16, Page 11
Subclass 6.9 Target Organ Systemic Toxicity	Part V, Chapter 17, Page 10
Subclass 9.1 Aquatic Ecotoxicity	Part VI, Chapter 19, Page 18
Subclass 9.2 Soil Ecotoxicity	Part VI, Chapter 20, Page 8
Subclass 9.3 Terrestrial Vertebrate Ecotoxicity	Part VI, Chapter 21, Page 7
Subclass 9.4 Terrestrial Invertebrate Ecotoxicity	Part VI, Chapter 22, Page 5

Identity of the Active Ingredient

As this is the first full Part 5 application considered for this active ingredient, general data about metrafenone are provided in the Tables A2.3 and A2.4.

Table A2.3: Identification of metrafenone.

	CAS number: 220899-03-6
IUPAC name	(3-bromo-6-methoxy-2 methylphenyl)(2,3,4-trimethoxy-6-methylphenyl)-methanone
Common name	Metrafenone
CAS number	220899-03-6
Molecular formula	$C_{19}H_{21}O_5Br$
Molecular weight	409.3
Structural formula	Refer to figure 1
Purity	97% nominal 94% minimum
Significant impurities/additives (% concentration)	See confidential appendix
Known uses	Fungicide
HSNO classification	**6.7B, 9.1D (biocide)**
Other classification & labelling	

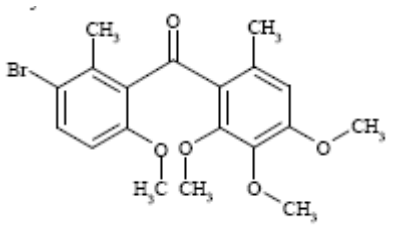


Figure 1: Structural formula of metrafenone.

Physical and chemical properties of metrafenone relevant to the interpretation of ecotoxicity test, environmental fate and exposure assessment are summarised in Table A2.4.

Table A2.4: Physical and chemical properties of metrafenone.

Property	Metrafenone	Test method	Reference
Colour	AC 375839 (Technical Grade Active) Yellow – white solid	OPPTS 830.6302	Werle 1999 Study No. 9850400411A GLP Klimisch score: 1
Colour	AC 375839 (CL 375839) (Secondary standard) White to chalky	OPPTS 830.6302	Werle, 1998 Study No. 985040042A GLP Klimisch score: 1
Physical state	AC 375839 (CL 375839) (Technical Grade Active) Powdery, fine crystalline solid	OPPTS 830.6303	Werle, 1999 Study No. 9850400411B GLP Klimisch score: 1
Physical state	AC 375839 (CL 375839) (Secondary standard) Crystalline solid	OPPTS 830.6303	Werle, 1998 Study No. 985040042B GLP Klimisch score: 1
Odour	AC 375839 (CL 375839) (Technical Grade Active) Low intensive musty smell	OPPTS 830.6304	Werle, 1999 Study No. 9850400411C GLP Klimisch score: 1
Odour	AC 375839 (CL 375839) (Secondary standard) Low intensive musty smell	OPPTS 830.6304	Werle, 1998 Study No. 985040042C GLP Klimisch score: 1
Vapour pressure	AC 375839 1.53×10^{-4} Pa (20°C) 2.56×10^{-4} Pa (25°C)	OECD 104 OPPYS 830.7950	Yacoub, 2001 Stduy No. 81807 GLP Klimisch score: 1
Henry's Law constant K_H dimensionless	BAS 560F 5.42×10^{-5}	Calculation	Beigel 2002 Study No. EXA 01-058
Melting range	AC 375839 (CL 375839) (Secondary standard) Range (mean) 99.2 – 100.8°C	EC Method A1	Werle, 1998 Study No. 985040042D GLP Klimisch score: 1
Boiling Point	AC 375839 (CL 375839) (Secondary standard) Up to the max. temperature of ca 310°C no boiling point was observed.	EC Method A2	Werle, 1998 Study No. 985040042E GLP Klimisch score: 1
Relative Density (20°C)	AC 375839 (CL 375839) (Technical Grade Active)	EC Method A3	Werle, 1999 Study No. 985040411D

	1.45 g/cm^3		GLP Klimisch score: 1
Relative Density (20°C)	AC 375839 (CL 375839) (Secondary standard) 1.45 g/cm^3	EC Method A3	Werle, 1999 Study No. 995040804 GLP Klimisch score: 1
Water Solubility (mg/L)	AC 375839 Deionized water: 0.474 pH 5: 0.552 pH 7: 0.492 pH 9: 0.457	EC Method A6 OECD 105	Yan, 1998 Study No. ENV 98-010 GLP Klimisch score: 1
Solvent Solubility (20°C) (mg/L)	AC375839 Acetone: 403000 Acetonitrile: 165000 Dichloromethane: 1950000 Ethyl Acetate: 261000 n-Hexane: 4800 Methanol: 26100 Toluene: 363000	EC Method A6 OECD 105	Sicilia & Ta, 1998 Study No. ENV 98-023 GLP Klimisch score: 1
Log Kow	4.3 (Kow: 19950) May have the potential for bioaccumulation	OPPTS 830.7570 OECD117	Holman, 1999 Study No. ENV 98-043 GLP Klimisch score: 1
Dissociation constant	A dissocation constant does not exist in the pH range of 2 to 12. This is consistent with the chemical structure of AC375839. Since there are no dissociable hydrogens present.	OECD 112	Petry 1998 Non-GLP Klimisch score: 2
Flammability	AC 375839 (CL 375839) (Technical Grade Active) Not highly flammable according to the cited EC council directive.	EC Method A10	Werle, 1999 Study No. 985040411F GLP Klimisch score: 1
Autoflammability	AC 375839 (CL 375839) (Technical Grade Active) Not self-igniting according to the cited EC council directive.	EC Method A16	Werle, 1999 Study No. 985040411G GLP Klimisch score: 1
Explosive properties	AC 375839 (CL 375839) (Technical Grade Active) Not an explosive agent according to the cited EC council directive.	EC Method A14	Werle, 2002 Study No. 1999-084 GLP Klimisch score: 1
Surface Tension	AC 375839 (CL 375839) (Technical Grade Active) 67.4 mN/m (20°C) (90% saturated aqueous solution) Is not regarded as surface active according to the cited guideline.	EC Method A5	Werle, 1999 Study No. 985040411E GLP Klimisch score: 1
Oxidizing properties	AC 375839 (CL 375839) (Technical Grade Active)	EC Method A17	Werle, 1999 Study No.

	No oxidizing properties under the conditions of the test and according to the cited guideline.		985040411H GLP Klimisch score: 1
Photochemical oxidation rate	203.5904 x 10^{-12} cm^3/molecule-sec Using a global OH concentration of 1.5 x 10^6 OH/cm^3 with a 12 hr day, the tropospheric half-life is calculated to be 0.63 hours.	Atmospheric Oxidation Program	Mangels, 2001 Study No. EXA 01-037 GLP Klimisch score: 1
Metabolites			
Property	**4082230 (CL377160)**	**Test method**	**Reference**
Water Solubility (mg/L)	Deionized water pH 4.0: 1.1 pH 2.8: 1.0 pH 11.6: 175	EC Method A6 OECD 105	Daum, 2001 Study No. PCP06308 GLP Klimisch score: 1
Property	**4084564**	**Test method**	**Reference**
Log Kow	3.52 (Estimated) More hydrophilic than parent and therefore less likely to bioconcentrate in organisms. (Calculated Log Kow of BAS 560 F = 5.16)	Calculation	Martin, 2002 Study No. ENV 02-011 Klimisch score: 1
Property	**CL 375816**	**Test method**	**Reference**
Log Kow	neutral pH: 3.01 ionized: -1.09 More hydrophilic than parent and therefore less likely to bioconcentrate in organisms. (Calculated Log Kow of BAS 560 F = 5.16)	Calculation	Martin, 2002 Study No. ENV 02-012 Klimisch score: 1

Biological Hazards: Class 6 Toxicity

Formulations containing metrafenone have not previously been considered in detail under Part 5 of the HSNO Act. The Agency has summarised new publicly available information relating to the toxicity of metrafenone (Table A2.5).

Metrafenone is a new pesticidal active ingredient to New Zealand. In addition to toxicity studies on Vivando, the applicant has provided toxicity studies on metrafenone (Table A2.5). A summary of the studies taken into consideration in the determination of the Acceptable Operator Exposure Level (AOEL) and Acceptable Daily Exposure (ADE) is provided in Table A2.6. Formulation data for Vivando (500 g ai/L SC) is provided in Table A2.6a.

Table A2.5: Summary of toxicity data on metrafenone[8].

ACUTE TOXICITY		
Acute oral toxicity	**Acute dermal toxicity**	**Acute inhalation toxicity**
SPECIES: Rats STRAIN: Sprague-Dawley derived (Crl:CD(SD) BR) NO. OF ANIMALS /SEX/GROUP: 5 ENDPOINT: LD_{50} TEST SUBSTANCE: AC375839 REMARKS: There were no mortalities, nor were there clinical signs of toxicity. All animals gained weight. VALUE: > 5,000 mg/kg bw GLP: Yes TEST GUIDELINE: OECD No 401 (1987), US EPA OPPTS 870.1100, 92/69/EEC, B.1 (1992). REFERENCE SOURCE: Lowe, C.A. 1999. Oral LD_{50} study in albino rats with AC375839. Toxicology Report A99-33(BN/411/001) BASF DocID 1999/7000303. RELIABILITY (KLIMISCH SCORE): 1	SPECIES: Rats STRAIN: Sprague-Dawley derived. Crl:CD(SD) BR NO. OF ANIMALS/SEX/GROUP: 5 ENDPOINT: LD_{50} TEST SUBSTANCE: AC375839 REMARKS: There were no mortalities, nor were there clinical signs of toxicity. All animals gained weight. VALUE: >5000 mg/kg bw/day GLP: Yes TEST GUIDELINE: OECD No 402. US EPA OPPTS 870.1200. 92/69/EEC B3. REFERENCE SOURCE: Bradley, D. 1999. Dermal LD_{50} study in albino rats with AC375839. Toxicology Report A99-32 (BN/412/001) BASF DocID 1999/7000301. RELIABILITY (KLIMISCH SCORE): 1	SPECIES: Rats STRAIN: Sprague-Dawley derived. Crl:CD(SD) BR NO. OF ANIMALS/SEX/GROUP: 5 ENDPOINT: LC_{50} TEST SUBSTANCE: AC375839 DOSE LEVEL: The average exposure concentration was 5.00 mg AC375839/L. Exposure was nose only for 4 hours. The average mass median aerodynamic diameter was 3.103 with a geometric standard deviation of 1.949. Size distribution of particles was: 4.67% ≤1.90 microns 65.16% ≤4.0 microns 95.80 5 ≤10 microns. REMARKS: The only clinical sign of toxicity during the exposure period was laboured breathing in up to 4 animals. Immediately following exposure the signs included red nasal discharge, excessive salivation, chromodacyrorrhea, dried red material in the facial area, laboured breathing and moist rales. These signs were seen for the first few days after exposure. All but one animal had entirely recovered by the end of the 2nd week. In conclusion the substance was practically non toxic at the treated dose. VALUE: >5.00 mg/L GLP: Yes TEST GUIDELINE: OECD No 403. US EPA OPPTS 870.1300. 94/79/EEC B2. REFERENCE SOURCE: Hoffman, G.M. 2000. Acute inhalation toxicity study with AC375839 in rats via nose-only exposure. Toxicology Report A99-128 (BN/413/001) BASF DocID 2000/7000119. RELIABILITY (KLIMISCH SCORE): 1 The Agency does not consider that the respiratory effects, from which all but one animal recovered rapidly, should be considered a significant toxic effect justifying a 6.1E classification.
Conclusion on Classification: No classification	***Conclusion on Classification: No Classification***	***Conclusion on Classification: No Classification***

[8] In this table two company code names (AC375839 and BAS 560F) are used for metrafenone. The former code is obsolete.

IRRITATION	
Eye irritation	**Skin irritation**
SPECIES: Rabbits STRAIN: New Zealand White NO. OF ANIMALS/SEX/GROUP: 6 males TEST SUBSTANCE: AC375839 RESULTS: Negative. There were no signs of corneal opacity or iris effects. Conjunctival irritation was observed at the 1 hour observation in all animals, and in 2/6 at the 24 hour observation, with grade of 1.0. The overall EEC mean scores for corneal opacity, iris effects, conjunctival redness and conjunctival irritation at 24, 48 and 72 hours were: 0.0, 0.0, 0.1 and 0.0 respectively. GLP: Yes TEST GUIDELINE: OECD No 405. US EPA OPPTS 870.2400. 92/69/EEC B.5. REFERENCE SOURCE: Boczon, L, 1999. Primary eye irritation study in albino rabbits with AC375839 (BN/415/001) BASF DocID 1999/7000298. RELIABILITY (KLIMISCH SCORE): 1	SPECIES: Rabbits STRAIN: New Zealand White NO. OF ANIMALS/GROUP: 6 males TEST SUBSTANCE: AC375839 RESULTS: Negative. The erythema and oedema scores were both 0.0. The primary irritation index (PII) was 0.0 GLP: Yes TEST GUIDELINE: OECD No 404. US EPA OPPTS 870.2500. 92/69/EEC B.4. REFERENCE SOURCE: Boczon, L, 1999. Primary dermal irritation study in albino rabbits with AC375839 (BN/415/002) BASF DocID 1999/7000295. RELIABILITY (KLIMISCH SCORE): 1
Conclusion on classification: No classification	***Conclusion on classification: No classification***
SENSITISATION	
Respiratory sensitization	**Contact sensitization**
	SPECIES: Guinea pigs STRAIN: Crl: (HA)BR NUMBER OF ANIMALS/SEX/GROUP: 20 in the test, and 10 in the control group. TEST SUBSTANCE: AC375839 RESULT: Negative. REMARKS: Irritation pre-screening was done with 4 animals via intradermal injection and a further 4 animals as a topical application at 1, 10 and 25% of the test substances in carboxymethylcellulose (CMC) /Tween 80. Based on the screening, the intradermal injection in the test phases was 1% in CMC/Tween 80 and 25% in CMC/Tween 80 for the topical for induction and 10% in CMC/Tween 80 for the challenge phase. The method of Magnusson and Kligman was used. None of the test or control group animals exhibited a dermal reaction to the challenge application of the text or control materials. GLP: Yes TEST GUIDELINE: OECD No 406. US EPA OPPTS 870.2600. 94/79/EEC B.6. REFERENCE SOURCE: Glaza, S.M., 1999. Primary dermal irritation study in albino rabbits with AC375839 (BN/416/001) BASF DocID 1999/7000304. RELIABILITY (KLIMISCH SCORE): 3 (not reliable) The Agency notes that the reliability of this study is questionable, due to the low concentrations of the test substance used in the study. The Agency would have preferred at least the use of 25% for

	both induction and challenge. Nevertheless, this does not raise concerns for the application since formulation data are available for Vivando (see Table A2.6a).
Conclusion on classification: Insufficient data.	***Conclusion on classification: Insufficient data***
MUTAGENICITY	
***In vitro* studies**	***In vivo* studies**
STUDY TYPE: Bacterial reverse mutation assay CELL TYPE: Bacterial cells (*Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 and *Escherichia coli* strain WP2 uvrA. TEST SUBSTANCE: AC375839 (purity 95.86%) in dimethyl sulfoxide as solvent DOSE RATE: 0, 25, 50, 100, 250, 500, 1000, 2500 and 5000 µg/plate RESPONSE: Negative with and without s9 metabolic activation. REMARKS: Generally precipitate was observed with dose levels ≥1000 µg/plate, but no appreciable toxicity was observed. TEST GUIDELINES: US EPA OPPTS 870.5100 94/79/EEC REFERENCE SOURCE: Wagner V.O. and Sly J.E. 1999. Bacterial reverse mutation assay with AC375839. (BN/435/001) BASF DocID 1999/7000326 RELIABILITY (KLIMISCH SCORE): 1	STUDY TYPE: *In vivo* test for micronucleated polychromatic erythrocytes in bone marrow of mice. SPECIES: Mice NUMBER OF ANIMALS/SEX/GROUP: 3 in range finding study and 5 in the assay. TEST SUBSTANCE: AC375839 (purity 95.86%) DOSE RATE: Range finding study: 10, 50, 100, 500, 1000 and 2000 mg/kg bw. Assay 500, 1000 and 2000 mg/kg bw in both sexes. RESPONSE: Negative REMARKS: There was no statistically significant increase in the number of micronucleated polychromatic erythrocytes in the treatment group at any dose level or harvest time compared to the concurrent vehicle control groups. TEST GUIDELINE: ICH Harmonised tripartite Guideline S2A Guidance on specific aspects of regulatory genotoxicity tests for pharmaceuticals (1995). REFERENCE SOURCE: Xu, J. 2001. AC 375839: *In vivo* test for chemical induction of micronucleated polychromatic erythrocytes in mouse bone marrow cells. (BN/435/002) BASF DocID 2001/7000268. RELIABILITY (KLIMISCH SCORE): 2 (The Agency notes that compliance with standard test guidelines, OECD, OPPTS or EU was not established.)
STUDY TYPE: Gene mutation induction test in cultured Chinese hamster ovary cells CELL TYPE: Chinese hamster ovary cells TEST SUBSTANCE: BAS 560F DOSE RATE: 0.1 – 5000 µg/mL The definitive assay and confirmatory assay used test article concentrations of 17, 50, 167, 500 1667, and 5000 µg/mL (with and without activation). RESPONSE: Negative in the CHO/HGPRT Gene Mutation Assay. REMARKS: Test article concentration of ≥50 µg/ml formed precipitate in the treatment media in tests both with- and without- metabolic activation, indicating the solubility limit of the test article had been exceeded. In the non activated system the number of mutants/1x10^6 surviving cells for DMSO (solvent controls) were 0-3. In the test the ration was 1- 12 (but all replicates at 17 µg/mL were lost due to contamination).	

In the metabolic activated system the number of mutants/$1x10^6$ surviving cells for DMSO and acetone (solvent controls) were 0-5. In the test the ratio was 0-6. Positive controls gave increases of 405 and 390 for ethyl methansulfonate (EMS) and 311 and 363 for 7, 12-dimethylbenz(α)anthracene (DMBA). In the non-activated system at 1667 µg/mL there was a statistically significant response in the confirmatory assay, but the solvent control value was unusually low. In comparison to historical controls the test was less than double the control value. TEST GUIDELINES: US EPA OPPTS 870.5300. OECD No 476. 94/79/EEC REFERENCE SOURCE: Pant K.M. 2001. BAS 560F: Test for chemical induction of gene mutation at the HGPRT locus in cultured Chinese hamster ovary cells with and without metabolic activation with a confirmatory assay. (BN/435/003) BASF DocID 2001/7000288. RELIABILITY (KLIMISCH SCORE): 1	
STUDY TYPE: Chromosomal aberration assay in cultured Chinese hamster ovary cells CELL TYPE: Chinese hamster ovary cells TEST SUBSTANCE: BAS 560F DOSE RATE: 5.0 – 250 µg/mL in range finding study, 10, 12.5, 25, and 100 µg/mL in the test without metabolic activation and 10, 12.5, 125 and 250 µg/mL in the test with metabolic activation. RESPONSE: Negative both with and without metabolic activation. TEST GUIDELINES: US EPA OPPTS 870.5375. OECD No 473 (1997) 94/79/EEC B.10 REFERENCE SOURCE: Xu, J. 2001. BAS 560F: Test for chemical induction of chromosomal aberration in cultured Chinese hamster ovary cells with and without metabolic activation. (BN/435/004) BASF unpublished report DocID 2001/7000340. RELIABILITY (KLIMISCH SCORE): 1	
Conclusion on classification: No classification.	
CARCINOGENICITY	
TYPE OF STUDY: 24 month dietary toxicity and oncogenicity study in rats SPECIES: Rats STRAIN: Sprague-Dawley derived, Crl: CD(SD)IGS BR NO.ANIMALS/SEX/GROUP: 75 (10 for interim sacrifice at the end of Month 12) TEST SUBSTANCE: BAS 560F (purity 95.86%) DOSE LEVELS: 0, 500, 5,000, 20,000 ppm. Due to reduced body weight gain (>40% reduction in comparison to controls), and microscopic findings at interim sacrifice, the top dose for <u>female</u> rats was reduced to 10,000 ppm from Week 69. [The Agency noted that due to the reduced dose rate for top females, it would have been useful if the researchers has estimated an average intake for these female animals] Mean substance intakes were 24.9 (male), 30.4 (female), 260.0 (male), 320.2 (female), 1068.5 (male), 1418.6 (female) mg/kg bw/day for the 500, 5000 and 20,000 ppm groups respectively. The intake in	

the top dose female treated with 10,000 ppm in the 2nd 12 month period (approximately) was 592.8 mg/kg bw/day.
ROUTE: Oral in diet
GLP: Yes
TEST GUIDELINES: OECD No 453 (1981). EPA OPPTS 870.4300 (1998). 87/302/EEC No. L 133/37-42 (1988)
REMARKS: Chronic toxicity
See comment above about reduced body weight gain and microscopic findings at interim sacrifice at 12 months. Researchers reducing the top dose for females to 10,000 ppm from Week 69.

No treatment-related clinical findings were found.

Ophthalmoscopic examination at Month 12 and 24 did not reveal any effect due to the treatment.

Mean body weights and body weight gains of females administered 5,000 and 20,000/10,000 ppm and of males administered 20,000 ppm were significantly decreased relative to controls after 24 months of treatment. The overall body weight gains were reduced by 26 and 42% respectively in the mid and top dose females respectively, and by 14% for the top dose males at 24 months.

Food consumption was comparable or slightly higher in treated animals than controls.

No neurobehavioural adverse effects were seen based on the functional observational battery or motor activity evaluations.

Small increases in clotting parameters, mean prothrombin time and mean activated partial thromboplastin, were seen a 3, 6, 12 and 18 months particularly in males at 5000 ppm and above, but the degree of prolongation of clotting reduced with time through the study and there was no effect at termination. The Agency concluded that the changes are not a significant toxicological effect, although they are likely to be compound-related.

There were some small disturbances in red cell parameters (mean haemoglobin, haematocrit and erythrocyte count) for females at 5000 ppm and above at 3, 6 9 and 12 months. While the laboratory's grading of the changes increase from marginal to moderate at 12 months, the effects did not persist throughout the study. There were no differences between treatment and control groups at termination. [The Agency did not consider these changes to be a significant toxicological effect of the test substance.

From Month 12 elevated GGT and lower bilirubin levels were apparent in males receiving 5000 or 10000 ppm and after Month 18 these were accompanied by higher cholesterol levels. The magnitude of changes in the mean values appeared to increase with duration of exposure particularly for the GGT, but this was heavily influenced by a highly raised value in one animal. [At termination this animal had a value of 35U/L, while all other animals in the same group had values <10 U/L].

On all or most occasions of sampling during the study elevated total protein, calcium, cholesterol and GGT levels were apparent for females receiving 5000 or 20,000/10,000 ppm. The magnitude of the increase for cholesterol did not further progress after 12 months. While an apparent progression in the elevation of GGT appeared in the mean values this was influenced by highly elevated values in two animals.

Increases in liver weights and histological changes were seen in the liver which were associated with the clinical chemistry observations (serum liver enzyme, cholesterol and albumin concentration changes). Central lobular hepatocellular hypertrophy and eosinophilic hepatocellular alteration and a dose-related increase in incidences of non-zonal vacuolation (female only) and basophilic heptocellular alteration (female only) were seen. The effects in females were more severe than males and there was an increased incidence of central lobular necrosis and hepatocellular polyploidy in females only.

Table: Incidences of centrilobular hypertrophy (males) and centrilobular hypertrophy/ polyploidy/eosinophilic alteration/epithelial hyperplasia (females)

	Control	Group 2	Group 3	Group 4
Males	**0**	**500**	**5,000**	**20,000**
Terminal Sacrifice	0	2	6	15
Unscheduled Deaths	1	0	5	14
Females	**0**	**500**	**5,000**	**20,000/10,000**
Terminal Sacrifice	0/0/3/13	1/1/4/20	20/15/17/25	29/33/29/35
Unscheduled Deaths	0/0/0/12	1/0/1/7	13/9/8/16	12/13/10/13

Benign hepatocellular adenoma incidence in females was 1/75, 0/75, 6/75 and 12/75 for the controls, 500, 5,000 and 20,000/10,000 ppm dose groups respectively One female (20,000/10,000) with a benign adenoma also had a malignant hepatocellular carcinoma.

In males, there was a slight increase in the incidence of benign hepatocellular adenoma 4/75 in the 20,000 ppm group in comparison to controls (1/75). Researchers did not consider this increase was treatment-related as the incidence is within historical control incidence. One malignant heptocellular carcinoma occurred in each of the top and control groups in males.

Urinalysis revealed increased protein levels in Months 6, 12, 18 and 24 in top dose females in comparison to controls. There changes correlated with the histopathology findings in kidney (see Table below). Males and females administered 5,000 and 20,000/10,000 ppm had increased kidney weights and an increased incidence of subacute/chronic interstitial inflammation/chronic nephropathy of the kidney. Females dosed 20,000 10,000 had the highest incidence of these kidney changes and they correlated with increases in BUN and urinary protein levels after 12, 18 and 20 months of treatment.

Table: Incidence of subacute/chronic interstitial inflammation/chronic nephropathy of the kidney

	Control	Group 2	Group 3	Group 4
Males	**0**	**500**	**5,000**	**20,000**
Terminal Sacrifice	18	16	18	21
Unscheduled Deaths	22	27	34	41
Females	**0**	**500**	**5,000**	**20,000/10,000**
Terminal Sacrifice	7	6	26	42
Unscheduled Deaths	9	15	22	19

Other microscopic findings in females were also seen. There was an increased incidence of parathyroid hyperplasia at top dose level terminal animals and in the top two doses for unscheduled deaths. Incidence of epithelial squamous cell hyperplasia and cornification of the cervix was increased at terminal sacrifice (23/44) in comparison with controls (3/26) in the 10,000 ppm females. (The increase was partly attributed by researchers to enhanced survival of the animals at this dose level. The finding was not considered of toxicological significance.)

Survival of treated animals was generally comparable with controls although the high dose female animals had higher survival (44/65) than control females (26/64) which was attributed to the reduced body weight gain.

The researchers comment as follows on the metabolic activation of the compound. BAS 560F belongs to the class of chemistry referred to as a benzophenone. Biochemical data from 13 week studies in rat and mouse by the US National Toxicology Program (NTP) indicate that benzophenone is a relatively potent inducer of the phenobarbital-type (2B) cytrochrome P450 enzyme. Overall the induction was greater in rats than in mice. The gross (organ weight) and microscopic (hepatocellular hypertrophy) changes can be an indication of increased pentoxyresorufin dealkylase activity. (See the end of this table for studies relating to liver induction and its reversibility). [The Agency notes that the data in the liver metabolism study are not consistent with the above summary as pentoxyresorufin dealkylase activity was only slightly increased in female animals and was not considered a significant finding.]

a. Non-neoplastic effects
LOAEL: 5000 ppm (equivalent to 260 mg/kg bw/day in males and 320 mg/kg bw/day in females)
Reduced body weight gain in females, microscopic changes in liver and kidney (males and females).

The histological changes were:
liver: primarily centrilobular hepatocellular hypertrophy and eosinophilic hepatocellular alteration (some necrosis in females);
kidney: subacute/chronic interstitial inflammation/chronic nephropathy.
NOAEL: 500 ppm (equivalent to 24.9 mg/kg bw/day in males and 30.4 mg/kg bw/day in females)

b. Neoplastic effects
LOAEL: 5000 ppm (equivalent to 260 mg/kg bw/day in males and 320 mg/kg bw/day in females)
Increased incidence of benign hepatocellular adenoma in females only)
NOAEL: 500 ppm (equivalent to 24.9 mg/kg bw/day in males and 30.4 mg/kg bw/day in females)
mg/kg bw/day)

TUMOURS: benign hepatocellular adenoma (females only)
MALIGNANT/ BENIGN: Benign
INCIDENCE IN CONCURRENT CONTROLS: 1/75
TIME OF ONSET: No information
SURVIVAL: The survival analysis reflected a tendency to greater survival of top dose female animals than expected (likely to be due to reduced body weight gain). Thus tumours did not adversely affect survival.
DOSE/ RESPONSE: Yes
REFERENCE SOURCE: Kelly C.M. 2002. A 24 month dietary toxicity and oncogenicity study with BAS 560F in rats BN/428/001 BASF DocID 2002/7004381
RELIABILITY (KLIMISCH SCORE): 2

Agency review: The Agency notes that the anaemia in females and an effect on clotting did not persist to termination of the study.

The researchers did not consider the increase in benign hepatocellular adenoma in males to be treatment-related, although the incidence (5.3%) is slightly above the historical control rate at this laboratory (4.0%). Data were provided from the Huntingdon Life Sciences database to indicate that this incidence is well within historical ranges for this strain of rat. Lang, 1992 reports 1.3–18.2% for hepatocellular adenoma. Giknis and Clifford (2001) reported 1.43 – 8.0% in males of this strain.

The Agency notes that one review of background rates indicated zero incidence of adenocarcinoma in females of this strain, but the other studies reported the overall incidence as 0.4% (range in various studies: 1.0 – 4.0%) and 0.77 (range in various studies: 0.77 – 1.67%). The Agency concluded that the 1/75 seen at 20,000/10,000 ppm in the current study is not outside the background incidence for adenocarcinoma in females of this strain.

The study report does not contain a summary table documenting tumour findings by site by sex and treatment group. Nevertheless, the liver tumours are clearly set out in the summary. Other tumour types are said to be within historical incidence. The Agency notes that no other significant tumour sites in the rat are listed in the US EPA summary data sheet for metrafenone, which supports the study conclusion.

The Agency notes that taking into account the historical data, the only increased incidence of tumours is for benign hepatocellular adenoma in female rats.

TYPE OF STUDY: 18 month oncogenicity in mice
SPECIES: Mice
STRAIN: Crl: CD1 (ICR)BR
NO.ANIMALS/SEX/GROUP: 65 (due to an early death and replacement there were 66 male mice in the 7,000 ppm dose group)
TEST SUBSTANCE: BAS 560F (purity 95.86%)
DOSE LEVELS: 0, 250, 1,000 and 7,000 ppm (Intakes were 39, 156, and 1109 mg of BAS 560F/mg bw/day for males and 53, 223, and 1493 mg of BAS 560F/mg bw/day for females.
ROUTE: Oral in diet
GLP: Yes
TEST GUIDELINES: OECD No 451. US EPA OPPTS 870.4200. 87/302/EEC

REMARKS:
No clinical signs of toxicity were observed during the study period. Survival was not adversely affected by administration of the test substance (there was a tendency to longer survival at higher dose).

Food consumption values for both sexes were comparable with the concurrent controls.

There were no adverse effects of treatment on body weight.

No treatment related haematological changes were found in either sex at any dose at either 12 months or at termination.

Statistically significant increases in absolute and relative (to body weight) liver weight were noted for males at 7,000 ppm and for females at 1,000 and 7,000 ppm in comparison to controls. The other treated groups had comparable absolute and relative liver weights. The response in females at 1,000 and 7,000 ppm demonstrated a dose-response relationship.

Hepatocellular hypertrophy (diffuse or centrilobular) was noted in the livers of males receiving 1,000 ppm and both males and females receiving 7,000 ppm. In male mice a dose-response in the incidence was seen.

In kidneys an increased incidence and severity of chronic nephropathy was noted in males receiving 1,000 or 7,000 ppm and in females receiving 7,000 ppm compared to control mice.

An increase in the incidence of extramedullary haematopoiesis in the spleens of female mice (only) was seen at 7,000 ppm.

A statistically significant increase (P >0.01) in the incidence (19/66) of primary hepatocellular neoplasms (adenomas and carcinomas) was seen in the livers of male mice receiving 7,000 ppm in comparison to controls (6/65). The table below summarises the liver tumour data for adenomas and carcinomas.

There was a marginal increase in the incidence of primary hepatocellular neoplasm (adenomas and carcinomas) of females receiving 7,000 ppm (4/65) compared to control females (2/65). [Two carcinomas in the top dose in females, but none seen at lower dose.]

Table: Incidence of primary hepatocellular neoplasms (adenomas and carcinomas). The bracketed values indicate the number of adenomas/carcinomas in each case.

Sex	Control	250 ppm	1,000 ppm	7,000 ppm
Males	6/65 (4/2)	3/65 (2/1)	9/65 (8/1)	19/66 (14/5)
Females	2/65 (2/0)	1/65 (1/0)	1/65 (1/0)	4/65 (2/2)

a. Non-neoplastic effects
LOAEL: 1,000 ppm (approximately 1109 mg/kg bw/day for males and 1493 mg/kg bw/day for females). Based on increased liver weights in females and chronic nephropathy and hepatocellular hypertrophy in males.
NOAEL: 250 ppm (equivalent to 39 mg/kg bw/day for males and 53 mg/kg bw/day for females)

b. Neoplastic effects
LOAEL: 7,000 ppm (approximately 1,109 mg/kg bw/day in males and 1,493 mg/kg bw/day in females) based on increased incidence of primary heptocellular neoplasms (adenomas and carcinomas) in male mice.
NOAEL: 1,000 ppm (approximately 156 mg/kg bw/day for males and 223 mg/kg bw/day for females)

TUMOURS: Heptocellular neoplasms (adenomas and carcinomas)
MALIGNANT/ BENIGN: Mixed.
BACKGROUND INCIDENCE: 6/65 (in this study)
TIME OF ONSET: Report implies earlier onset in males
SURVIVAL: No effect on survival seen.
DOSE/ RESPONSE: Not clearly demonstrated.
REFERENCE SOURCE: Fischer, J. 2002. 18 month dietary oncogenicity study in albino mice with BN/428/001 Study T-1130 (BN/428/002) BASF DocID 2002/70044834
RELIABILITY (KLIMISCH SCORE): 1

In conclusion the Agency notes that the substance caused both benign and malignant tumours in male mice and that that these did not affect survival.

Conclusion on classification: 6.7B

Based on a weight of evidence approach, as described below, the Agency assigned a 6.7B classification to metrafenone.

On both the rat and mouse carcinogenicity studies higher than control and /or background incidences of liver tumours were reported at the high level. The Agency notes that in the rat that the tumours were benign and confined to high level females which were deemed to be treated above the Maximum Tolerated Dose (MTD) and that in the mouse the higher incidence was seen in high level males only, although the tumours were both benign and malignant.

In the rat study the increased incidence of liver tumours was confined to females at a level which was above the MTD as indicated by a substantial effect on bodyweight; the extent of the bodyweight effect was such that after Week 69 of treatment the dose level was reduced by 50% (10,000 ppm from 20,000 ppm). Thus the researchers claimed that it was inappropriate to use these data in the assessment of carcinogenicity. However the Agency notes that there was also a substantial effect on bodyweight gain for females at the intermediate dose (and a slight increase in the incidence of liver tumours), indicating a level also above the MTD, this then only leaves one dose level which is 10 times below the intermediate level to assess the carcinogenicity potential in female rats. On the basis of only one level of females being below the MTD the Agency consider that the data from the rat carcinogenicity study should be interpreted with caution.

On the mouse carcinogenicity study complications with respect to excessive toxicity were not encountered. Thus the complete study was considered fit for purpose. If there was no evidence of increased tumor formation on this mouse study, then the results of the rat study at levels above the MTD would be disregarded and a 6.7 classification would not be triggered, especially as the tumours in the rat were benign in nature. However the high level mice did exhibit a higher than control and background incidence of both benign and malignant tumours. This provides weight that a 6.7 classification should be given.

In order to counteract claims of carcinogenic potential the researchers put forward a proposed mechanism of action i.e proposed that the higher incidence of liver tumours in rats and mice was mediated through induction of the Phenobarbital-type (2B) cytochrome P450 enzyme; a mechanism which has been shown not to be associated with elevated incidences of liver tumours in humans. However based on a review of the hepatic enzyme study performed to support this claim (further details of this study are given at the end of this table) and taking into consideration the results of a similar study performed with phenobarbitone, the Agency considers this claim is not adequately supported. Both of these investigative studies measured ethoxyresorufin O-depentylase (EROD) and pentoxy resorufin O-depentylase (PROD). In the study with BAS 560F, EROD was increased by approximately 17 and 10 fold for males and females respectively, whilst PROD was only induced by approximately 1.5 fold and then only in females. In contrast, in the phenobarbitone study EROD was

induced by approximately 3-fold in males only whilst PROD was increased by approximately 18 and 25-fold respectively in males and females. Thus the profile of induction varies between the two test substances and therefore the Agency concluded that there was insufficient evidence to support the claim that the increased incidence of liver tumours in the rat and mouse carcinogenicity studies with BAS 560F were a result of a mechanism which is considered irrelevant to humans.

The researchers' also performed a S-phase response and a foci initiation study in rats. The S-phase study indicated that the test substance has the ability to cause cell proliferation in a short period of time which showed progression over time. (The grading of centrilobular hepatocyte hypertrophy going from minimal to slight after 1 week to minimal to moderate after 4 weeks of treatment). In addition, in females, which is the sex where the liver tumors were evident in this species, liver weight increased from +13% of controls to +50% controls over the period Week 1 to 4, which again indicates that the test substance is a potent inducer of cell proliferation. This supports the possibility of the test substance being classed as carcinogenic, working via a promotion type activity.

The final study the researchers performed to investigate the potential for carcinogenesis was a foci initiation study. The conclusion of this study was that BAS 560F does not have initiating potential.

Carcinogenesis is a multistage process which is commonly accepted to comprise 3 easily recognizable steps: initiation; promotion; progression. The Agency notes that the researchers have provided some limited data that BAS 560F is not a tumour promoter however the information from the carcinogenicity studies and the S-phase study indicate that it may elicit carcinogenicity buy acting as a promoter.

Further evidence to support the Agency's 6.7B classification is that on several toxicity studies in a variety of species the liver is identified as a target organ, indicating that the liver is prone to damage by this test substance. One response to damage is by cell proliferation and regeneration which can escalate out of control and result in tumour formation.

In the absence of sufficient evidence to support the claim that the mode of action is irrelevant to humans but evidence to suggest this test substance does target the liver and increases cellular proliferation, the Agency considers there is **sufficient evidence to support a 6.7B classification**.

This classification is generally consistent with the US EPA data summary which states "Suggestive evidence of carcinogenicity". The US EPA has multiple levels of classification of carcinogenic potential, whereas HSNO has two classifications: 6.7A Known or presumed human carcinogen; 6.7B Suspected human carcinogen.

REPRODUCTIVE/DEVELOPMENTAL TOXICITY

Developmental studies

STUDY TYPE: Developmental study in rats
SPECIES: Rat
STRAIN: Crl: CD(SD)IGS BR
NO/SEX/GROUP: 25 female/group
DOSE: 0, 50, 500, and 1000 mg/kg bw/day (day 6-20 of gestation).
ROUTE: Oral by gavage.
TEST SUBSTANCE: BAS 560F (formerly AC 375839) (purity not stated)
GLP: Yes
TEST METHOD: OECD No 414. US EPA OPPTS 870.3700. 94/79/EEC. Annex II 5.6.2

REMARKS: Maternal body weights, gravid uterine weights, body weight changes and feed consumption values were unaffected by treatment.

A slight statistically significant increase in the ratio of liver weight to body weights occurred in the 1000 mg/kg bw/day dose group. There were no associated macroscopic or microscopic changes in the liver so the body weight changes were not considered by researchers to be of toxicological significance.

No litter parameters were affected by doses of the test substance as high as 1000 mg/kg bw/day. Litter averages for corpora lutea, implantation, litter sizes, live fetuses, early and late resorptions, fetal body weights, percent resorbed conceptuses and percent live male fetuses were comparable among treated and control groups.

There were no dose-dependent or significant differences in the litter or fetal incidences of any gross external, soft tissue or skeletal alterations.

DEVELOPMENTAL STUDIES

MATERNAL TOXICITY
NOAEL: 1000 mg/kg bw/day
LOAEL >1000 mg/kg bw/day (no adverse effects identified)

FOETAL TOXICITY
NOAEL: 1000 mg/kg bw/day
LOAEL: > 1000 mg/kg bw/day (no adverse effects identified)

REFERENCE SOURCE: Barnett, J.F. 2001. A definitive oral developmental toxicity (embryo-fetal toxicity/teratogenicity) study with BAS 560F in rats. (BN/432/002) BASF DocID 2001/7001372
RELIABILITY (KLIMISCH SCORE): 1

STUDY TYPE: Developmental study in rabbits
SPECIES: Rabbit
STRAIN: New Zealand White (Hra: NZW SPF)
NO/SEX/GROUP: 25 female/group
DOSE: 0, 50, 350, and 700 mg/kg bw/day (day 6-28 of gestation).
ROUTE: Oral by gavage.
TEST SUBSTANCE: BAS 560F (formerly AC 375839) (purity not stated)
GLP: Yes
TEST METHOD: OECD No 414. US EPA OPPTS 870.3700. 94/79/EEC. Annex II 5.6.2

REMARKS: Three deaths occurred during the study but these were not attributed to the test substance. One rabbit in the control group and one in the 700 mg/kg bw/day group were found dead, while another rabbit in the control group was sacrificed moribund. These deaths were attributed to intubation accidents and in two of the three deaths the injuries were clearly consistent with this cause of death. In the other case the litter appeared normal and there was no other cause of death determined.

The only treatment-related clinical sign was scant faeces in the 700 mg/kg bw/day group.

Liver weight and ratio of liver to body weight was increased in 350 and 700 mg/kg bw/day groups. This was statistically significant and there was a dose-relationship.

Maternal body weight gains were significantly reduced in the 350 and 700 mg/kg bw/day groups for the entire dosing period and gestation period.

Absolute and relative feed consumption values were generally significantly reduced in the 350 and 700 mg/kg bw/day groups for the entire dosing period.

Microscopic examination showed increased incidence and severity of periportal hepatocellular hypertrophy in 350 and 700 mg/kg bw/day groups and there was a dose response relationship. The affected periportal hepatocytes were enlarged with an increased amount of densely eosinophilic, finely granular cytoplasm. There was an increased incidence and severity of diffuse heptocellular cytoplasmic vacuolation in the 350 and 700 mg/kg bw/day groups, but such vacuolation was seen to varying degrees in all groups including controls. The liver histological findings correlate with the liver weight changes.

One and two rabbits respectively in the 350 and 700 mg/kg bw/day groups delivered on Gestation Day 29. Researchers noted that the deliveries could not be ruled out as being treatment related, but noted these 3 does delivered on GD29.

There were no gross external, soft tissue or skeletal fetal alterations (malformations or variations) caused by doses of BAS 560F as high as 700 mg/kg bw/day. There was no effect of the substance on litter or fetal incidences of any gross external, soft tissue or skeletal alterations.

There was a slight, statistically significant reduction in fetal body weights in the 700 mg/kg bw/day dose group.

DEVELOPMENTAL STUDIES

MATERNAL TOXICITY
NOAEL: 50 mg/kg bw/day
LOAEL 350 mg/kg bw/day based on reduced body weight gain and feed consumption, increase absolute and relative liver weights and microscopic changes in the liver.

FOETAL TOXICITY
NOAEL: 350 mg/kg bw/day
LOAEL: 700 mg/kg bw/day based on reduced fetal body weights

REFERENCE SOURCE: Barnett, J.F. 2001. A definitive oral developmental toxicity (embryo-fetal toxicity/teratogenicity) study with BAS 560F in rabbits. (BN/432/001) BASF DocID 2001/7001288
RELIABILITY (KLIMISCH SCORE): 1

The Agency notes that the effect on fetal body weight occurs at dose levels well above the maternal NOAEL. In the absence of any other corroborative findings on the fetuses this disturbance in bodyweight gain is considered not a developmentally significant finding but most likely to be an indirect effect of maternal toxicity. The Agency notes that there may be a slight effect on gestation length [possibly in both rats and rabbits], but this was equivocal.

Reproductive studies

STUDY TYPE: Two generation study in rats
SPECIES: Rats
STRAIN: Crl: CD(SD)IGS BR
NO/SEX/DOSE: 30
TEST SUBSTANCE: BAS 560F
ROUTE: Oral in diet
DOSE: 0, 500, 1,000 and 10,000 ppm. The intakes were equivalent to 39, 79 and 811 mg BAS 650F/kg bw/day for the pre-mating parental P generation. Mean test substance intake (for females) during gestation was 36.8, 73.0 and 720.3 mg BAS 650F/kg bw/day. The substance intakes during lactation were 70.7, 140.4 and 1264.2 mg BAS 650F/kg bw/day.
TEST METHODS: OECD No 416 (draft 1998), US EPA OPPTS 879.3800. 94/79/EEC Annex II 5.6.1
REMARKS: One 500 ppm P generation male animal died on Day 92. The cause of death was not determined. In the absence of any other deaths in treated animals, including higher levels, this death is considered not to be attributable to treatment.

No clinical effects of toxicity of the substance were seen during the study on P generation males or females.

Body weight and body weight gain was reduced in the parental P animals at 10,000 ppm during the pre-mating period and then generally throughout the study period and the changes were statistically significant in Weeks 1-11.

Overall food consumption was not affected by treatment in P males, although there was a slight reduction in food consumption in the first two weeks of the study in 10,000 ppm P females possibly attributable to palatability. There was a reduction in food consumption in P females at 10,000 ppm and this correlated with the reduced body weight parameters. There were a few weeks where food consumption was reduced to a statistically significant extent in 1,000 ppm females but this was not consistent from week to week and there was no effect on body weight or body weight gain at this dose.

Parental toxicological effects in P and F1 generations included signs of anaemia (based on reduced erythrocytes, reduced haemoglobin concentration and hematocrit) for the 10,000 ppm group in both males and females which was more pronounced in females and possibly treatment-related.

The general toxic effects in parental animals were the increased absolute and relative (to body weight) liver weights with associated microscopic changes seen in 10,000 ppm group. At 1000 ppm increase

relative liver weight was seen in females but this was not considered by researchers to be treatment-related. Decreases in relative spleen and thymus weights in comparison to body weight and grain weight in pups in the 10,000ppm dose group were considered by researchers to be related to the smaller size of the pups. Absolute and relative spleen weights were reduced for 1000 ppm males and females and 500 ppm females, but researchers did not consider these changes treatment-related due to the absence of a dose-response. [The Agency considered the changes were likely to be within normal variation.]

There was no effect on oestrous cycle. There was no effect on fertility indices or time to mating that was treatment-related.

The number of P females with litters was not affected by treatment nor was there any effect on litter size at birth or on number of stillborn pups. A slight statistically significant reduction in gestation length (21.9 days vs 22.3 days) in 10,000 ppm P females in comparison to controls was not considered by researchers to be of toxicological significance. [The Agency notes no equivalent finding was seen in the F1, however a similar effect was suggested in the rabbit developmental study.]

The effect on body weight and food consumption continued during lactation for the 10,000 ppm female animals. The substance intakes during lactation were 70.7, 140.4 and 1264.2 mg BAS 650F/kg bw/day.

The body weights of F1 pups of both sexes for the 10,000 ppm group were reduced at birth and through to weaning, with the difference from concurrent controls (8%) at birth increasing to a 31% reduction at weaning.

There were no clinical signs attributed to the test compound in F1 pups. However, in one litter at 10,000 ppm, pups were emaciated and cool to touch, and showed reduced activity. The incidence of these findings is given in the table below. (For data relating to F2 generation see below.)

Clinical findings in F1 pups

	Control	**500 ppm**	**1,000 ppm**	**10,000 ppm**
Emaciated	0/384	0/353	0/411	14/399
Reduced activity	0/384	0/353	1/411	13/399
Skin cool to touch	0/384	1/353	0/411	6/399

There was a delay in sexual maturation seen as delayed vaginal opening in F1 parental females at 10,000 ppm (34.7 days) in comparison to controls (32.4 days). Researchers attributed this to developmental delay reflected in body weight reduction during lactation and post weaning and therefore did not identify this as a direct treatment-related developmental effect. [The Agency is not convinced that this finding is not of toxicological significance, but considers the evidence equivocal and insufficient to justify classification in isolation.]

In the F1 parental males there was no change in the mean age for preputial separation.

In the F1 parental generation 3 deaths occurred (2 males at 500 ppm and one at 10,000 ppm) which were not considered treatment related. One male in the 500 ppm was found at necropsy to have a perforated palate due to injury, and this was considered by researchers to be the cause of death. The other 500 ppm male was euthanized with impaired hind limb function. (Researchers did provide further information on the cause.) The male animal in the 10,000 ppm group at necropsy had dilated renal pelves, and hydronephrosis was confirmed microscopically. One female animal in the 500 ppm group was sacrificed in extremis with an adenocarcinoma of the mammary tissue (also affecting the spleen).

Body weight and body weight gain was reduced in both the 1000 ppm and 10,000 ppm dose group males, with the changes evident earlier in the higher dose. In females the body weight and body weight gain reduction only affected the 10,000 ppm group.

No effect on F1 parental female oestrous cycle parameters.

There was no effect on mating and fertility indices for F1 females.

Gestation weight in the 10,000 ppm F1 females was reduced, but the body weight gains were unaffected during gestation. Reduced food intake in the 10,000 ppm group was consistent with pre-mating parameters, but the toxicological significance was not clear since no reduction in gestation body weight gain was seen.

There was no effect of the substance on the parturition data for the F1 females. [The Agency notes that the slightly shorter gestation length seen in the P females at 10,000 ppm was not seen in the F1 generation.]

Body weight and food consumption during lactation was reduced in the 10,000 ppm F1 females.

For F1 females substance intakes during lactation were 68.3, 140.2 and 1371.7 mg BAS 650F/kg bw/day.

Litter parameters were comparable with controls for treated groups in F2 litters.

Mean anogenital distance for F2 pups were comparable to controls

F2 pup body weights in the 10,000 ppm group were reduced at birth and throughout lactation. The reduction seen at some time periods for F2 pups at 500 ppm were not considered treatment-related in the absence of changes at 1000 ppm.

Sex ratio and pup survival in the F2 pups was unaffected by treatment.

Table: Clinical findings in F2 pups

	Control	**500 ppm**	**1,000 ppm**	**10,000 ppm**
Emaciated	0/292	2/354	0/301	6/270
Reduced activity	2/292	1/354	1/301	18/270
Skin cool to touch	0/292	1/354	0/301	6/270

Overall, considering the data for the F1 generation above, there does not appear to be a clear dose response for these findings, particularly when it is recognized that the affected pups in F1 are littermates. [However, the Agency considered that the clinical findings in the top dose animals cannot be discounted as being treatment related and of toxicological significance.]

Liver findings referred to for the P generation were also reflected in the findings for the F1 and F2 generations. The liver was the clearly the primary target organ for the substance from the point of view of microscopic and organ weight changes, but some variations in the spleen and thymus absolute and relative weights were seen, without corresponding microscopic findings.

The sperm parameters for the P males did not reveal any change in progressive motility or in the percentage of abnormal sperm at any dose. Sperm data for F1 indicated a statistically significantly lower percentage of progressively motile sperm in the 10,000 ppm group. Also, the percentage abnormal sperm was increased in this group (2.09%) versus controls (0.21%), predominantly in appearance of sperm hook (either absence or excessive). Although these findings are suggestive of an adverse treatment-related affect, no changes in reproductive performance and other sperm parameters were seen.

PARENTAL TOXICITY
NOAEL: 500 ppm (approximately 39 mg/kg bw/day)
LOAEL: 1,000 ppm (approximately 79 mg/kg bw/day), based on reduced body weight and body weight gain in P parental females and F1 parental males and females. (Additional findings at higher dose.)

REPRODUCTIVE EFFECTS
NOAEL: 10,000 ppm (approximately 811 mg/kg bw/day)
LOAEL: No adverse effect.

DEVELOPMENTAL TOXICITY
NOAEL: 1,000 ppm (approximately 79 mg/kg bw/day)
LOAEL: 10,000 ppm (approximately 811 mg/kg bw/day) effect on body weight and absolute and relative liver weight, possibly some developmental effects seen in clinical signs of emaciation, reduced activity and cool to touch.

REFERENCE SOURCE: Schroeder, R.E. 2002. A two generation reproduction study with BAS 560F in rats. (BN430/002) BASF DocID 2002/7004752
RELIABILITY (KLIMISCH SCORE): 1

The Agency considers the findings for reproductive and developmental toxicity are not sufficient to justify classification for reproductive toxicity, because the effects occur at doses well above the maternal NOAEL. Nevertheless, the Agency notes that is some evidence of clinical toxicity in the top dose F1 and F2 pups, and there was an increase in incidence of sperm abnormalities in the F1 which may indicate an effect which increases with duration of treatment. Since there was no effect on mating behaviour or fertility, the toxicological importance of the sperm effects is unclear. There was also a suggestion of a developmental delay in female pups.

Conclusion on classification: No classification

TARGET ORGAN SYSTEMIC TOXICITY

Subchronic toxicity – oral

TYPE OF STUDY: 28 day dietary toxicity in rats
SPECIES: Rat
STRAIN: Charles River, Sprague Dawley derived (Crl: CD(SD)BR)
NO.ANIMALS/SEX/GROUP: 5 (The top dose group actually consisted of 4 males and 6 females. On Day 7 one male was found to be a female and reassigned to the female group.)
TEST SUBSTANCE: BAS 560F
DOSE LEVELS: 0, 1000, 5000, 10,000, and 20,000 ppm (in diet). The average intakes were 106, 528, 1127 and 2245 mg of BAS 560F/kg bw/day for males and 118, 586, 1151 and 2294 mg of BAS 560F/kg bw/day for females.
ROUTE: Oral (in diet)
GLP: No
TEST GUIDELINES: OECD No 407. 67/548/EEC B
REMARKS: There were no deaths and there were no clinical signs of toxicity in either sex at any dose level in the study. The food consumption values were generally comparable (or in excess of) control animals. The body weights and body weight gains were also generally comparable with controls for most measurement intervals.

There were no effects on haematological parameters.

Clinical chemistry revealed an increase in total cholesterol in female rats from 1000 ppm and above. The increase at 5000 ppm was associated with microscopic periportal cytoplasmic vacuolation so the finding at this dose was considered adverse, in contrast to that at 1000 ppm where the increase was only seen in 2/5 female rats and was not associated with any microscopic findings.

Increase liver weight was seen in both sexes at 5000ppm and above. The liver weight relative to body weight was also increased in these dose groups.

Macroscopic findings included discolouration of the liver in 3/5 females as 10,000 and 2/6 at 20,000 ppm.

Periportal cytoplasmic vacuolation was seen in females treated with 5,000 ppm or more and in males at 20,000 ppm.

There were no signs of necrosis.

LOAEL: 5000 ppm (528 mg/kg bw/day in males and 586 mg/kg bw/day in females) based on increase absolute and relative (to body weight) liver weight, increased total cholesterol and increased incidence of cytoplasmic vacuolation of the liver in females. (In males the changes were not associated with clinical chemistry or microscopic changes at this dose, but there was a slight increase in liver weight.)

NOAEL: 1000 ppm (106 and 118 mg/kg bw/day respectively in males and females). [See Agency comment about this NOAEL below.]

REFERENCE SOURCE: Fischer, J.E. 2001. 28 day dietary toxicity in albino rats with BAS 560F. T/1009 (BN/420/002) BASF DocID 2001/7000267.
RELIABILITY (KLIMISCH SCORE): 2

The Agency notes that while 5000 ppm was considered not to produce an adverse effect in male liver, the NOAEL of 1000 ppm was attributed to both sexes in the report's conclusion. The Agency is not convinced of the researcher's NOAEL in this study. The Agency notes that cytoplasmic vacuolation in the liver is typical of fatty change which is commonly considered to be an indication of toxicity which is often reversible. However in the absence of evidence of reversibility this change has been classed as adverse on this study. Also in the 13 week study with recovery there was not full recovery with respect to hepatocyte vacuolation.

TYPE OF STUDY: 28 day dietary toxicity in dog
SPECIES: Dog
STRAIN: Beagle
NO.ANIMALS/SEX/GROUP: 2
TEST SUBSTANCE: AC375839
DOSE LEVELS: 0, 500, 1000, 10,000 and 20,000 ppm in diet initially, but this was terminated. All animals were returned to control diet after 4 days, until body weights returned to control values. The substance was then administered by capsule at 12.5, 25, 250 and 500 mg/kg bw/day for a period of at least a further 28 days (See comment below: These dose levels are approximately equivalent to the intake that would have been achieved based on the dietary concentration). (Control animals received empty gelatin capsules.)
ROUTE: Oral in diet changed to capsule administration
GLP: Yes
TEST GUIDELINES: No guidelines exist for 28 day dog study
REMARKS: Poor food consumption and a decrease in body weight were seen in the top two doses, so the dietary administration was terminated after four days and the dietary administration replaced with gelatin capsules as described above.

During the first week of treatment at 500 mg/kg bw/day (by capsule) there was loss of body weight and body weight gain in the animals was reduced, but this did not persist during the remaining 3 weeks of treatment.

There was no effect of treatment on food consumption, physical condition or ophthalmic examination or urinalysis.

Absolute and relative liver weight was increased slightly in the top dose animals at termination, but as there were no associated histopathology findings this was not considered by researchers to be of toxicological significance.

LOAEL: 500 mg/kg bw/day (in the capsule phase) due to reduced body weight and body weight gain early in the study.
NOAEL: 250 mg/kg bw/day (in the capsule phase)
REFERENCE SOURCE: Kelly C.M, 1999. 28 day oral toxicity study in with AC375839 in purebred beagle dogs via capsule administration. (BN/420/001) BASF DocID 1999/7000325
RELIABILITY (KLIMISCH SCORE): 2

Agency: The Agency notes the NOAEL proposed by researchers is 250 mg/kg bw/day due to the initial effect on body weight of capsule dosing. Due to the reversibility of this effect the Agency considers this NOAEL would be more appropriately based on the liver weight changes seen at termination, but the establishment of a firm NOAEL for the 28 day study is not necessary. A decision on the significance of the liver weight effects would be best considered as part of a longer term study in dogs (see below). This is a preliminary study with only 2 dogs per sex per dose as a range finding study, so assigning an NOAEL is not appropriate, particularly for relatively small body weight effects.

The Agency notes the report does not include detailed information on the dietary phase of the study. Although it is not stated directly the Agency assumes that the capsule dosing was necessary due to a

palatability of the diet in dogs. Note that using the dietary dose equivalence for the dog (0.025 mg/kg bw/day per 1 ppm) (ERMA New Zealand, 2008, Registry of Toxic Effects of Chemical Substances, US Department of Health Human Services, 1997), the original dietary dose levels 0, 500, 1000, 10,000 and 20,000 ppm were equivalent to approximately 0, 12.5, 25, 250 and 500 mg/kg bw/day. (The 90 day and 1 year dog studies also employed capsule dosing.)

TYPE OF STUDY: 13 week toxicity (with 28 day recovery phase) in rats
SPECIES: Rat
STRAIN: Charles River, Sprague Dawley derived (Crl: CD(SD)BR)
NO.ANIMALS/SEX/GROUP: 10 (5 males and females in addition in the control and top dose for the recovery phase)
TEST SUBSTANCE: BAS 560F (This study documents on p9 that two company codes names, AC375839 and BAS560F are used to refer to this active ingredient. The former is stated to be an obsolete company code name.)
DOSE LEVELS: 0, 1000, 5000, 10,000, and 20,000 ppm (in diet). The average intakes were 0, 79, 404, 800 and 1663 mg of BAS 560F/kg bw/day for males. The average intakes were 0, 94, 486, 967 and 1938 mg of BAS 560F/kg bw/day for females.
ROUTE: Oral (in diet)
GLP: Yes
TEST GUIDELINES: OECD No 408. 67/548/EEC B. US EPA Test Guideline 82-1
REMARKS: There were two deaths that were accidental and not related to treatment. There were no clinical signs of toxicity.

Body weights for both sexes were generally comparable or in excess of control rats at most measurement intervals. During the second part of the study female animals at 5,000, 10,000 and 20,000 ppm tended to show lower weekly bodyweight, in comparison with controls which resulted in the overall weight gain being 14.6%, 14.6% and 13.2% respectively. Weight gains for the 10,000 ppm groups were generally comparable or greater than controls during the recovery phase.

Changes in haematological parameters at termination were decreased haemoglobin and mean corpuscular haemoglobin concentration (MCHC) in females for the top two dose groups, and decreased mean corpuscular haemoglobin (MCH) at 10,000 only. There was also a reduced platelet count in top dose females.

After the recovery phase there was a decrease in the white blood cell counts in male animal previous dosed at 20,000 ppm and an increase in platelets in female animals previous dosed at 20,000 ppm.

The researchers noted that these findings were for one sex only, and were within historical control values. The changes were not associated with histopathological change, so the researchers considered the changes incidental and unrelated to treatment.

Clinical chemistry revealed slight, but statistically significant increases in cholesterol and total protein in both sexes at 20,000, 10,000 and 5,000 ppm at termination. Albumin values were slightly increased in female rats only in the 20,000 ppm animals.

At the end of the 28 day recovery period, there was a trend towards these parameters returning to control levels, suggesting that the findings were an adaptive response of the liver (according to researchers).

At termination, a statistically significant increase in urinary protein was seen in males at 10,000 and 20,000 ppm compared to controls. The values are within the laboratory reference range for this age and strain of rat. Researchers considered the change not to be treatment-related.

Increased absolute and relative (to body weight) liver weights were seen in both sexes at 5000 ppm and above at termination and these changes were statistically significant. For males and females at 1000 ppm only very slight increases in these parameters were seen, and only the relative liver weights for males were increased to a statistically significant degree.

The increase in absolute and relative liver weights at 5000 and 10,000 ppm for females and for both sexes at 20,000 ppm were considered treatment-related because they correlated to microscopic changes (see below). These microscopic changes were not seen at 1000 ppm,

At the end of the 28 day recovery period, the absolute and relative liver weights were comparable in the animals previously dosed at 20,000 ppm and controls.

Other organ weight changes were increased relative adrenal weight in females at 5,000, 10,000 and 20,000 ppm , increased relative heart weights in females at 1,000, 5,000, 10,000 and 20,000 ppm and increased absolute and relative kidney weight in both sexes at 10,000 and 20,000 ppm and at 5,000 ppm in females only. [These changes were not associated with microscopic changes and thus are not considered to be of toxicological importance.]

There were no treatment-related macroscopic pathological changes.

Microscopic findings were found in the liver only. In females treated at 5,000 10,000 and 20,000 ppm periportal cytoplasmic vacuolation consistent with accumulation of lipid was seen. This finding was equivocal in males only at the top dose. No dose-response relationship was evidence in the incidence or severity of this finding in females.

After the 28 day recovery phase, the males animals showed no histological changes with respect to periportal vacuolation, while only 2/5 females at the highest dose showed such changes to a slight/mild degree.

The liver changes were considered most likely to be an adaptive change by researchers, based on the response to the 28 day recovery both with respect to the liver weight and histopathology findings.

The pathology report notes the 28 day recovery with respect to the liver vacuolation and suggests that there is regression of this adverse effect after dosing for a longer period in comparison to the 28 day study.

LOAEL: 5,000 ppm (404 mg/kg bw/day in males and 486 mg/kg bw/day in females) based on increase cholesterol and total protein in both sexes, at and an increased incidence of microscopic cytoplasmic vacuolation of the liver in females only.

NOAEL: 1,000 ppm (79 and 94 mg/kg bw/day respectively in males and females).

REFERENCE SOURCE: Fischer, J.E. 2001. 13 week dietary toxicity and 28 day recover study in albino rats with BAS560F. T/1046 (BN/425/001) BASF DocID 2001/7000270.
RELIABILITY (KLIMISCH SCORE): 1

Agency: The recovery of the liver weight changes at top dose (20,000ppm) after the recovery phase was only partial. The Agency notes that the microscopic changes identified in the liver are typical of those associated with accumulation of fat and this view is supported by the researchers. Fat accumulation in the liver is a classical sign of liver toxicity, although usually reversible. As only partial recovery was seen in high level females after 4 weeks without treatment in the context of this study, this finding is considered to be indicative of toxicity.

TYPE OF STUDY: 13 week oral toxicity in rats (supplemental)
SPECIES: Rat
STRAIN: Charles River, Sprague Dawley derived (Crl: CD(SD)BR)
NO.ANIMALS/SEX/GROUP: 10
TEST SUBSTANCE: BAS 560F
DOSE LEVELS: 0, 250 and 500 ppm (in diet). The average intakes were 0, 21 and 43 mg of BAS 560F/kg bw/day for. The average intakes were 0, 24 and 48 mg of BAS 560F/kg bw/day for females.
ROUTE: Oral (in diet)
GLP: Yes
TEST GUIDELINES: OECD No 408. 67/548/EEC B. US EPA Test Guideline 82-1. The study report indicates that the reason for the supplementary study was in order to establish a NOEL for subchronic effects of the substance. [This justification may have been made while the main study was still in progress]
REMARKS: There was one death that was accidental and not related to treatment. There were no clinical signs of toxicity.

Body weights and body weight gains were generally comparable to those of control rats at most measurement intervals. Overall weight gains for male and female treated rats were generally comparable to those of control rats.

Food consumption was generally comparable to or in excess of those on control rats.

There were no treatment-related changes observed in either sex for either of the treated groups, with respect to haematological, clinical chemistry or urinalysis parameters at termination.

There were no treatment-related organ weight changes in either sex in the treatment groups, nor were there any macroscopic or microscopic changes that could be attributed to treatment with the test substance. Slight increases in absolute liver and spleen weights in males at 250 ppm were seen but the relative (to body weight) values were not raised, and no changes were seen at 500 ppm in either males or females.

An increase in heart weight relative (to body weight) in females only at 500 ppm was not considered treatment related as it was not associated with any microscopic change and was seen only in one sex.

There were no macroscopic or histological changes attributed to treatment with the test substance.

LOAEL: No effects established in this study.

NOAEL: 500 ppm (43 and 48 mg/kg bw/day respectively in males and females), the highest dose tested in this study.

REFERENCE SOURCE: Fischer, J.E. 2001. 13 week dietary toxicity in albino rats with BAS560F. T/1079 (BN/425/003) BASF DocID 2001/7000272
RELIABILITY (KLIMISCH SCORE): 1

TYPE OF STUDY: 13 week dietary toxicity study in mice
SPECIES: Mice
STRAIN: Albino Crl CD-1(ICR)BR
NO.ANIMALS/SEX/GROUP: 10
TEST SUBSTANCE: BAS560F (purity 97.1%)
DOSE LEVELS: 0, 1,000, 3,500 and 7,000 ppm in diet equivalent to 0, 163, 622 and 1206 mg/kg bw/day in males and 0, 216, 788 and 1663 mg/kg bw/day in females.
ROUTE: Oral
GLP: Yes
TEST GUIDELINES: OECD No 408. US EPA No 82-1. 67/548/EEC B
REMARKS: No treatment related mortality nor any clinical signs of toxicity were seen.

No affect on food consumption occurred.

A slight non statistically significant reduction in body weight was seen in the males at 7,000 ppm , commending from Week 5, but all other groups were comparable to controls.

The reduction in body weight gain in the 7,000 ppm males was not statistically significant, but was considered treatment-related by researchers.

For the other groups the body weight and body weight gains were comparable to those of the control mice.

No treatment-related haematological findings were seen at termination.

There were some variations seen in clinical chemistry parameters, total bilirubin in both sexes and 3,500 and 7,000 ppm, and increase cholesterol in females only at top dose. There were also sporadic reductions in albumin levels in the two top dose levels in females. [The Agency did not consider these variations indicative of significant toxicity from the test substance.]

Statistically significant increases in absolute and relative (to body weight) liver weights were seen in both sexes at 3,500 and 7,000 ppm. Very slight non statistically significant, increases in absolute and

relative (to body weight) liver weights at 1,000 ppm were considered treatment-related but were not considered by researchers to be adverse as there were no correlating microscopic findings. There were no other treatment related organ weight changes.

Microscopic examination of the livers revealed centrilobular hepatocellular hypertrophy in both sexes at 3,500 and 7,000 ppm. This change showed an increase in both incidence and severity with increasing dose and was correlated with the liver weight changes. No microscopic changes were seen in the animals treated at 1,000 ppm.

LOAEL: 7,000 ppm (equivalent to 1206 mg/kg bw/day in males respectively and 1663 mg/kg bw/day in females respectively), based on the view that no clearly toxicologically significant findings were identified
NOAEL: 3,500 (equivalent to 622 mg/kg bw/day in males respectively and 788 mg/kg bw/day in females respectively).
REFERENCE SOURCE: Fischer, J.E. 2001. 13 week dietary toxicity study in albino mice with BAS560F. T-1047 (BN/425/002) BASF DocID 2001/7000273.
RELIABILITY (KLIMISCH SCORE): 1

TYPE OF STUDY: 13 week dietary toxicity study in mice (supplemental)
SPECIES: Mice
STRAIN: Albino Crl CD-1(ICR)BR
NO.ANIMALS/SEX/GROUP: 10
TEST SUBSTANCE: BAS560F (purity 97.1%)
DOSE LEVELS: 0, 250, 500 ppm equivalent to 42 and 84 mg BAS 560F/kg bw/day for males and 55 and 113 mg BAS 560F/kg bw/day for females.
ROUTE: Oral in diet
GLP: Yes
TEST GUIDELINES: OECD No 408. US EPA No 82-1. 67/548/EEC B The study report indicates that the reason for the supplementary study was in order to establish a NOEL for subchronic effects of the substance.

REMARKS: Group mean body weights for females in the treated groups were reduced at some time points but these differences were not dose-related nor statistically significant. For the male animals the group mean body weights were generally comparable with controls.

The female animals in the 250 and 500 ppm showed a non-statistically significant reductions in weight gain of 20% and 15% compared to controls at the end of the study, respectively. Researchers did not consider these body weight reduction were treatment-related because they were no trend relating to dose, the difference was not statistically significant, and because no similar differences were seen in the other 90 day study in mice where treatment was up to 7,000 ppm.

Some variations in haemotological parameters (neutrophils, haemoglobin concentration and haematocrit) occurred, more commonly in females at 250 and 500 ppm, and an increase in cholesterol in males was detected at 500 ppm. Researchers considered these changes not to be treatment related in the context of laboratory control incidence. [While the Agency found some inconsistencies in the comparison with the historical data, the findings are not considered to be of toxicological importance.]

There were no changes in absolute or relative (to body weight) organ weight in either sex at any dose level in this study.

There were no findings of macroscopic pathology that were considered treatment related. A few alterations were found which are commonly seen in albino mice under laboratory conditions.

There were no microscopic changes observed that were related to the administration of the test substance.

LOAEL: No adverse effects reported in this study
NOAEL: 500 ppm (highest dose tested), equivalent to 84 mg/kg bw/day in male and 113 mg/kg bw/day in females.
REFERENCE SOURCE: Fischer, J.E. 2001. 13 week dietary toxicity study in albino mice with BAS 560F. Study T-1085 (BN/425/004) BASF DocID 2001/70001312.

RELIABILITY (KLIMISCH SCORE): 2

TYPE OF STUDY: 90 day dog
SPECIES: Dog
STRAIN: Beagle
NO.ANIMALS/SEX/GROUP: 4
TEST SUBSTANCE: AC 375839
DOSE LEVELS: 0, 50, 100 and 500 mg/kg bw/day 7 days per week
ROUTE: Oral in gelatin capsules (controls received an empty capsule)
GLP: Yes
TEST GUIDELINES: OECD No 409 (1998). EPA OPPTS 870.3150 (1996). 87/302/EEC Annex V (1988)
REMARKS: No clinical findings of significance were reported. Body weight, body weight gain and food consumption were also unaffected by treatment.

At the top dose an increase absolute and relative (to body weight) liver weight was seen in the male animals. In females absolute liver weights were slightly increased over control values, but only the increase in relative (to body weight) liver weight values were statistically significantly increased. (The Agency notes the limited value of statistical analysis for 4 animals.)

There were no corresponding macroscopic or microscopic changes in the liver so researchers did not consider the findings of toxicological significance.

LOAEL: None established. There was an increase in absolute and relative liver weight, but there were no histopathological findings, so the change was not considered adverse.
NOAEL: 500 mg/kg bw/day (the highest dose tested)
REFERENCE SOURCE: Kelly C.M. Fischer, 2001. 90 day oral toxicity study in with AC 375839 in purebred beagle dogs via capsule administration. Study T-1085 (BN/425/005) BASF DocID 2001/7000276
RELIABILITY (KLIMISCH SCORE): 1

TYPE OF STUDY: 1 year oral toxicity study in dogs
SPECIES: Dogs
STRAIN: Beagle
NO.ANIMALS/SEX/GROUP: 4
TEST SUBSTANCE: BAS 560F (purity 95.86%)
DOSE LEVELS: 0, 50, 150, and 500 mg/kg bw/day
ROUTE: Oral (in gelatin capsules). Control animals received empty capsules.
GLP: Yes
TEST GUIDELINES: OECD No 452 (1981). EPA OPPTS 870.4100 (1998). 87/302/EEC Annex V of EEC Directive 67/548/EEC (1988)
REMARKS: There were no clinical or physical findings considered to be related to the treatment.

The researchers concluded body weights were comparable between treated and control animals. [See Agency comment below]

The researchers concluded food consumption was comparable between treated and control animals. [See comment below]

Eye examinations did not indicate any treatment related ophthalmic effects.

There were occasional finding at haematological parameters at 6, 9 and 12 months time periods. These were marginal, of no clinical significance and generally within historical control data ranges.

There were no abnormalities associated with clotting parameters.

Urinalysis did not reveal any substance-related effects at 3, 6, 9 or 12 months.

There were mild increases in mean alkaline phosphatase levels in males dosed at 500 mg/kg bw/day after 9 and 12 months. There were primarily seen in 2 of 4 dogs and were not associated with abnormalities of other liver enzymes.

Other statistically significant differences in clinical chemistry were within the historical range and/or normal biological variation and not attributed to treatment.

Mean absolute and relative (to body weight) liver weights were statistically increased for high dose female animals, while only the relative weights were statistically significantly increased in high dose males.

There were no associated macroscopic or microscopic findings in the livers of either sex at the top dose level.

The researchers considered the changes seen in liver weight and alkaline phosphatase levels were not of toxicological significance.

LOAEL: > 500 mg/kg bw/day (no adverse effects identified)
NOAEL: 500 mg/kg bw/day (the highest dose tested).
REFERENCE SOURCE: Kelly C.M. 2001. One year oral toxicity study with BAS 560F in purebred beagle dogs via capsule administration. (BN/427/001) BASF DocID 2001/7001049.
RELIABILITY (KLIMISCH SCORE): 1

The Agency notes that treated female animals appeared to put on more weight and there appeared to be a slight dose-related trend for this. Related differences and trends in body weight gain were also seen. None of these changes reached statistical significance (according to the researchers), and no comment was made on the trend. [The Agency notes the limited value of statistical evaluation in small groups, and that review of the individual data indicates this is relatively consistent trend for the dogs in the groups, rather than an effect on mean values caused by outliers. Nevertheless, in the absence of associated pathology the Agency did not consider this of toxicological importance.]

The Agency reviewed the occasional clinical chemistry variations relating to: increased alkaline phosphatase (AlkP) concentrations (in males at 150 and 500 mg/kg bw/day at 9 months and termination and in females at 500 mg/kg bw/day at 9 months and termination); increased alanine amino transferase (ALT) concentrations (in females at 500 mg/kg bw/day at termination); and reduced potassium concentrations (in treated females only at 9 months). The Agency considered these variations were not of toxicological significance.

The NOAEL of 500 mg/kg bw/day proposed by the researchers was supported by the Agency. The Agency notes that OECD Test Guideline No 409 requires that the top dose level is associated with some toxic effects of significance, which was not achieved in this study. The Agency notes that this is not critical to the overall database, because the LOAELs in the 13 week and 2 year rat studies are below the NOAEL in this study.

Chronic toxicity/carcinogenicity

For chronic toxicity/carcinogenicity studies in rats and mice see data for 6.7 (carcinogenicity) classification above.

Conclusion on classification: No classification.

The LOAEL values for all studies are above the threshold for classification for repeat dose target organ toxicity (ERMA New Zealand, 2008, Table 17-2), with the single exception of the parental LOAEL for the 2 generation rat study at approximately 79 mg/kg bw/day.

The Agency notes that this is a 2 generation study of longer than a 90 day duration, so taking the duration into account and the overall dataset, the Agency does not propose any classification for repeat dose target organ systemic toxicity.

Absorption, Distribution, Metabolism and Excretion (ADME) studies

TYPE OF STUDY: ADME
SPECIES: Rat
STRAIN: Sprague Dawley (more definitive information not given)

NO.ANIMALS/SEX/GROUP: Various
TEST SUBSTANCE: ^{14}C labeled BAS 560F. Two labeled compounds were used, bromophenyl (6-^{14}C/6-^{13}C) and trimethoxyphenyl (U[9]-^{14}C/3-^{13}C) [Mass ratio of the two isotopes approximately 1:1 to assist in mass spectral analysis.]
DOSE LEVELS: Dose levels were 10 mg/kg bw (low dose) and 1000 mg/kg bw (high dose).
ROUTE: Oral gavage
GLP: Yes
TEST GUIDELINES: US 40 CFR 158 340. 94/79/EC, Annex IIA 5.1 (1994).

REMARKS: BAS 560F was not metabolized to volatile components (CO_2). The substance was readily absorbed. There were no substantial dose or gender differences in the absorption, distribution or elimination of either labeled compound. Most of the administered dose as excreted in faeces (84.1 – 99%) and to a much lesser degree urine (0.69 – 6.6%).

In a low-dose bile group, the majority of the radioactivity was eliminated in the bile indication that at least >88% of the applied dose was absorbed and the bilary excretion and metabolism are prominent processes. In the high dose bile group a smaller percentage (15 – 17%) of the applied dose was eliminated form bile and urine indicating a much lower percentage of dose absorption, presumably due to the saturation of absorption processes.

Accumulation of radioactivity in tissues was mainly observed in the gastrointestinal tract and its contents. Other tissues with higher total radioactive residue levels were liver, kidney, muscle, fat, adrenal and blood.

Very little residue remained in tissues 168 hours post dosing, although female tissues contained more radioactive residues than did male tissues. Since the total amount of residue was low the gender difference was not considered significant by researchers.

After oral administration absorption was quick and blood T_{max} was reached between 8.5 – 11 hours in lower dose and 14 – 15 hours in high dose groups. [The Agency does not consider the data support this researchers' conclusion. The peak blood levels suggest relatively slow absorption, although the proportion absorbed is high.] The elimination half-life ($T_{1/2elim}$) was between 39 – 43 hours (low dose) and 45 – 54 hours (high dose). AUC $_{(0-\infty)}$ was approximately 126 fold greater than the low dose group.

The label was mostly excreted as glucuronic acid conjugates in bile and urine indicating extensive metabolism. In faeces residues consisted primarily of the parent compound and aglycones of bile and urine conjugates.

The substance was extensively metabolized in fat, muscle, kidney and liver to several polar and non-polar metabolites.

The absorbed compound was metabolized in rats by O-dealkylation, aliphatic oxidation, debromination, ring hydroxylation and conjugation. The bond between the bromophenyl and trimethoxyphenyl ring remained intact.

REFERENCE SOURCE: Mullipudi, N. M., 2002. BAS 560F (AC 375839) absorption, distribution metabolisms and Excretion study in the rat. BASF DocID 2002/7005208.
RELIABILITY (KLIMISCH SCORE): 1

Liver metabolic activation studies

TYPE OF STUDY: Hepatic enzyme induction in rats for 4 weeks
SPECIES: Rat
STRAIN: Sprague Dawley (Crl:CD)
NO.ANIMALS/SEX/GROUP: 5
TEST SUBSTANCE: BAS 560F (purity 95.86%)
DOSE LEVELS: 0, 20,000 ppm (equivalent to 1,526 mg/kg bw/day in males and 1,654 mg/kg bw/day in females respectively)
ROUTE: Oral in diet.
GLP: Yes

[9] U represents uniform labelling of the carbon atoms in the trimethoxyphenol ring.

TEST GUIDELINES: No applicable guideline exists.
REMARKS: Ethoxyresorufin-O-deethylase (EROD) activity was markedly increased in males and females, approximately 17 and 10 fold for males and females respectively.

Glutathione concentration in liver was not affected after 4 weeks of treatment.

Pentoxyresofurin-O-depentylase (PROD) activity was statistically significantly increased only in female animals after 4 weeks, but the increase was small (1.5 fold) and was not considered by researchers to be of biological significance.

REFERENCE SOURCE: Mellert, W et al. 2002. Hepatic enzyme induction study in Sprague Dawley rats administration in the diet for 4 weeks. BASF DocID 2002/1005176.
RELIABILITY (KLIMISCH SCORE): 1

TYPE OF STUDY: S-phase response in rats (over 4 weeks with 2 week recovery)
SPECIES: Rats
STRAIN: Sprague Dawley (Crl:CD (SD) IGS BR)
NO.ANIMALS/SEX/GROUP: 8 with an additional 8 for the 20,000 ppm dose group for the recovery phase.
TEST SUBSTANCE: BAS 560F (purity 95.86%)

DOSE LEVELS: 0, 500 and 10,000 ppm in diet
ROUTE: Oral
GLP: Yes
TEST GUIDELINES: No applicable guidelines available.
REMARKS: One week prior to necropsy, osmotic minipumps containing bromodeoxyuridine (BrdU) were implanted subcutaneously in each animal. Cell proliferation (S-phase response), apoptosis and mitosis were evaluated in the liver (at necropsy).

At 20,000 ppm (approximately 1000 mg/kg bw/day) the summary of the findings is:

- Liver weight increased in both sexes
- Centrilobular hypertrophy of hepatocytes was seen
- Significant increases in cell proliferation in both sexes after 1 week of treatment occurred
- A significant increase of cell proliferation in females after 4 weeks of treatment occurred
- Zone 1 hepatocyes showed the most pronounced effect
- There was a reactive increase of apoptosis in females after 4 weeks of treatment and after a 2 week recovery period.

At 500 ppm (approximately 30 mg/kg bw/day) there were no substance related effects seen.

At 1 week, no effect on body weight was seen in males, but liver weights for the 20,000 ppm group increased (+13%). In females, there was a reduction in body weight at 500 ppm (-4%) and 20,000 ppm (-11%), while the liver weights increased at 20,000 ppm (+33%).

At 4 weeks, no effect on body weight was seen in either sex, but liver weights for the 20,000 ppm group females increased (+50%) and a small reduction of -13% was seen at 500 ppm. In the 20,000 ppm recovery animals, liver weight had fallen below controls weights after only 2 weeks in the female animals. There were no liver weight changes seen at 4 weeks in male animals at any dose, or in the recovery group.

At 1 week, centrilobular hypertrophy of the hepatocytes was seen in all male animals and in 5/7 females. Grading ranged from minimal to slight. (One top dose female animal had died on Day 3.)

At 4 week, centrilobular hypertrophy of the hepatocytes was seen in all male animals and in 7/8 females. Gradings ranged from minimal to moderate.

In the 4 week with 2 weeks recovery animals no histological findings were seen.

Cell proliferation in the liver was clearly increased after 1 and 4 weeks of treatment at 20,000 ppm in both sexes, with the effect more pronounced in females. Researchers claimed the 2 week recover

period resulted in full reversibility of the effect in both sexes. Researchers attributed the increase in apoptosis in female animals at the end of the 2 week recovery phase to a reactive response to the cell proliferation, so it was considered by researchers an indirect effect compound effect. REFERENCE SOURCE: Mellert, W et al. 2002. S-phase response study in the liver of Sprague Dawley rats. Administration in the diet for 1 and 4 weeks and recovery period of 2 weeks. BASF DocID 2002/1006201. RELIABILITY (KLIMISCH SCORE): 1
TYPE OF STUDY: Foci initiation test in rats (partially hepatectomised) SPECIES: Rats STRAIN: Sprague Dawley (Crl:CD (SD) IGS BR) NO.ANIMALS/SEX/GROUP: 12 TEST SUBSTANCE: BAS 560F (purity 95.86%) DOSE LEVELS: 5000 mg/kg bw (with and without 500 ppm of phenobarbitone (PB) in the diet as a promoter for 8 weeks beginning 2 weeks after treatment). Positive controls received 50 mg/kg bw of N nitrosomorpholine, (NNM) (with and without 500 ppm of phenobarbitone (PB) in the diet as a promoter for 8 weeks beginning 2 weeks after treatment). ROUTE: Oral GLP: Yes TEST GUIDELINES: No applicable guidelines available. REMARKS: The study included a control group, a positive control for foci initiation (using N nitrosomorpholine, NNM) and treatments with the test substance both with and without the promoter treatment of phenobarbitone (PB). In the positive control NNM, both with and without PB, a significantly increased number of glutathione-S-transferase-placental form (GST-P) positive foci was observed in comparison with controls. After treatment with BA560F there number of GST-P positive foci was very low and there was no significant difference from controls. Also the percental part of the foci area in comparison to the liver area did not show any difference. Therefore under the conditions of the study there was no indication of any initiating potential for the test substance. REFERENCE SOURCE: Mellert, W et al. 2002. BAS 560F Initiation study in Sprague Dawley rats. BASF DocID 2002/1006202. RELIABILITY (KLIMISCH SCORE): 1

Table A2.6 Summary of toxicity studies considered in determining the Acceptable Operator Exposure Level (AOEL) and Acceptable Daily Exposure (ADE) for metrafenone

Study	NOAEL	LOAEL	Critical effect
24 month toxicity and oncogenicity in rats	Chronic toxicity **500 ppm (24.9 mg/kg bw/day in males and 30.4 mg/kg bw/day in females**) Neoplastic 500 ppm (260	Chronic toxicity **5000 ppm (260 mg/kg bw/day in males and 320 mg/kg bw/day in females)** Neoplastic 5,000 ppm (260	Chronic toxicity Reduced body weight (in females), centrilobular hypertrophy (both sexes), eosinophilic hepatocellular alteration and some hepatocellular necrosis (females). Subacute/chronic interstitial inflammation/chronic nephropathy in the kidney in both sexes. Neoplastic Increase in benign

	mg/kg bw/day in males and 320 mg/kg bw/day in females)	mg/kg bw/day in males and 320 mg/kg bw/day in females)	hepatocellular adenoma in female rats only.
18 month mice	Chronic toxicity 250 ppm (39 mg/kg bw/day for males and 53 mg/kg bw/day for females) Neoplastic 1,000 ppm (156 mg/kg bw/day for males) and 223 mg/kg bw/day for females)	Chronic toxicity 1,000 ppm (1109 mg/kg bw/day for males and 1493 mg/kg bw/day for females) Neoplastic 7,000 ppm (1,109 mg/kg bw/day for males and and 1493 mg/kg bw/day in females)	Chronic toxicity Increased liver weight and extramedullary haematopoiesis in females and heptocellular hypertrophy and chronic nephropathy in males. Neoplastic Increase incidence of primary hepatocellular neoplasms (adenomas and carcinomas) in male mice (only).
Developmental study in rats	Maternal 1,000 mg/kg bw/day Foetal 1,000 mg/kg bw/day	Maternal >1,000 mg/kg bw/day Foetal >1,000 mg/kg bw/day	Maternal No adverse effects identified Foetal No adverse effects identified
Developmental study in rabbits	Maternal 50 mg/kg bw/day Foetal 350 mg/kg bw/day	Maternal 350 mg/kg bw/day Foetal 700 mg/kg bw/day	Maternal Reduced body weight gain and feed consumption, increased absolute and relative liver weight and periportal heptocellular hypertrophy. Foetal Reduced fetal body weight.
Two generation study in rats	Parental 500 ppm (approximately 39 mg/kg bw/day) Reproductive 10,000 ppm (approximately 811 mg/kg bw/day) Developmental 1,000 ppm (79 mg/kg bw/day)	Parental 1,000 ppm (approximately 79 mg/kg bw/day) Reproductive >10,000 ppm (approximately 811 mg/kg bw/day) Developmental 10,000 ppm (approximately 811 mg/kg bw/day)	Parental Reduced body weight and body weight gain (with liver toxicity at higher dose.) Reproductive No adverse reproductive effects identified. [The Agency noted effects on sperm in the F1generation.] Developmental Reduced body weight and increased liver weight. [The Agency noted clinical signs (emaciation, reduced activity and cool to touch) in F1 and F2 pups, and a suggestion of a pup developmental delay in F1 females pups that cannot be discounted as being treatment related and toxicologically significant.]
28 days in rats	1,000 ppm (106	5,000 ppm (528	Increase in absolute and

	mg/kg bw/day in males and 118 mg/kg bw/day in females)	mg/kg bw/day in males and 586 mg/kg bw/day in females)	relative liver weight (more severe in females), increased hepatocellular vacuolation in females.
13 week in rats (with recovery phase)	1,000 ppm (79 mg/kg bw/day in males and 94 mg/kg bw/day in females)	5,000 ppm (404 mg/kg bw/day in males and 486 mg/kg bw/day in females)	Increased cholesterol and total protein in blood, increase cytoplasmic vacuolation of the liver in females
13 week in rats (supplemental)	500 ppm (43 mg/kg bw/day in males and 48 mg/kg bw/day in females)	None demonstrated	None demonstrated [This study has been listed as although it is a supplemental study, it gave rise to the NOAEL used by the EU to derive its AOEL.
13 week in mice	3,500 (equivalent to 622 mg/kg bw/day in males and 788 mg/kg bw/day in females respectively).	7,000 ppm (1206 mg/kg bw/day in males and 1663 mg/kg bw/day in females)	Increased bilirubin and in absolute and relative liver weight with centrilobular heptocellular hypertrophy.
90 day dog and 1 year dog	500 mg/kg bw/day	>500 mg/kg bw/day	There was an increase in absolute and relative liver weight, but no histopathological findings, so not considered adverse.

Acceptable Operator Exposure Level (AOEL)

The Agency considered using the NOAEL from the 24 month toxicity oncogenicity study in rats (24.9mg/kg bw/day in males, rounded to 25 mg/kg bw/day) to establish the AOEL, due to the difficulty with dose level selection and the need for a supplemental study for the 13 week rat investigation. However, the Agency noted that the EU used the NOAEL from the supplemental 13 week rat study on which to base an AOEL of 0.43 mg/kg bw/day. The EU applied uncertainty factors applied: 100 (consisting of 10 for inter-species extrapolation and 10 for intra-species extrapolation). No correction for the AOEL the percentage of the substance absorbed in the study was applied. The Agency notes that in the case of metrafenone absorption at low dose was high. The absorption appeared to reduce at higher dose but this was not accurately quantified. The Agency also assumed 100% absorption, and established the AOEL on the same basis according to the following calculation:

$$\textbf{AOEL} = \frac{43 \text{ mg/kg bw/day} \times 1.0}{100} = \textbf{0.43 mg/kg bw/day}.$$

Acceptable Daily Exposure (ADE)

Study: 24 month toxicity oncogenicity study in rats, NOAEL 24.9 mg/kg bw/day in males (rounded to 25 mg/kg bw/day).

Uncertainty factors applied: 100 (consisting of 10 for inter-species extrapolation and 10 for intra-species extrapolation)

$$\text{ADE} = \frac{\text{NOAEL}}{\text{(uncertainty factors)}}$$

ADE = 25 mg/kg bw/day/100

ADE = 0.25 mg/kg bw/day.

The Agency notes that the EU established the ADI by the same approach.

Table A2.6a: Summary of Toxicity Data for the Formulated Product

ACUTE TOXICITY		
Acute oral toxicity	**Acute dermal toxicity**	**Acute inhalation toxicity**
SPECIES: Rat STRAIN: Sprague Dawley derived (Crl:CD(SD)BR) NO. OF ANIMALS/ SEX/GROUP: 5 ENDPOINT: LD_{50} TEST SUBSTANCE: AC 375839 500 g/L SC (RLF 12360) (undiluted) REMARKS: There were no deaths. There were no signs of toxicity in any animal. All animals gained weight. VALUE: >5000 mg/kg bw for both male and female animals. TEST GUIDELINES: US EPA OPPTS 870.1100; OECD No 401 (1987); 92/69/EEC B.1; REFERENCE SOURCE: C.A. Lowe, Oral LD_{50} study in albino rats with AC375839 500 g/L SC(RLF 12360) BASF (unpublished) DocID 2000/7000133. RELIABILITY (KLIMISCH SCORE): 1	SPECIES: Rat STRAIN: Sprague Dawley derived (Crl:CD(SD)BR) NO. OF ANIMALS/SEX/GROUP ENDPOINT: LD_{50} TEST SUBSTANCE: AC 375839 500 g/L SC (RLF 12360) (undiluted) REMARKS: There were no deaths. There were no signs of toxicity in any animal. All animals gained weight. VALUE: >5000 mg/kg bw for both male and female animals. TEST GUIDELINES: US EPA OPPTS 870.1200; OECD No 402 (1987); 92/69/EEC B.3 REFERENCE SOURCE: C.A. Lowe, Dermal LD_{50} study in albino rats with AC375839 500 g/L SC(RLF 12360) BASF (unpublished) DocID 2000/7000140. RELIABILITY (KLIMISCH SCORE): 1	SPECIES: Rat STRAIN: Sprague Dawley derived (Crl:CD IGS BR) NO. OF ANIMALS/SEX/GROUP:5 (ENDPOINT: LC_{50} TEST SUBSTANCE: AC 375839 500 g/L SC (RLF 12360) (diluted, aerosolised), 4 hour exposure nose only. The concentration achieved was 3.7 (3.3 – 3.9 mg/L). This was considered to be the highest achievable concentration. (Dilution 1;1 with distilled water was necessary to reduce viscosity prior to generation of the aerosol.) The mass median aerodynamic diameter was 5.2 µm, with a gravimetric SD of 1.728. On average 0.26% of particles were ≤ 1.0 µm, 30.64% were ≤ 4.0 µm, and 88.75% of particles were ≤ 10 µm. REMARKS: One animal was noted with laboured breathing after 1 hour of exposure. During the latter 2 hours of exposure one animal had chromodacryorrhea (coloured tears). There no other clinical signs of toxicity during the exposure period. (Wet fur was considered by researchers a normal finding in a nose-only exposure study to a liquid aerosol.) Following exposure, clinical signs included nasal discharge, chromodacryorrhea, decreased faecal volume and or yellow ano-genital staining in a few male and female rats for 2 days following exposures. No signs of toxicity were seen from Day 3 in males. Dried brown material in the faceal animal was seen in 2 females on Day 4. No signs of toxicity were seen in other females on Day 3, however occasional findings of red nasal discharge and alopecia were seen at various times during the 14 day observation period.

		VALUE: > 3.7 mg/L (gravimetric) TEST GUIDELINES: US EPA OPPTS 870.1300; OECD No 403 (1981); 92/69/EEC B.2 REFERENCE SOURCE: G.M. Hoffman, Acute inhalation toxicity study with AC375839 500 g/L SC(RLF 12360) in rats via nose only exposure. BASF (unpublished) DocID 2000/7000148 RELIABILITY (KLIMISCH SCORE): 1 The Agency notes that no significant signs of toxicity were seen at the highest achievable exposure concentration of 3.7 mg/L and considers no classification is appropriate.
Conclusion on Classification: No classification	***Conclusion on Classification: No classification***	***Conclusion on Classification: No classification***

IRRITATION

Eye irritation	**Skin irritation**
SPECIES: Rabbits STRAIN: New Zealand White NO. OF ANIMALS /GROUP: 3 (male) TEST SUBSTANCE: AC375839 500 g/L SC(RLF 12360) RESULT: Negative REMARKS: Individual mean scores at 24, 48 and 72 hours for corneal opacity and iris effects were both 0.0 for all animals. Individual mean scores at 24, 48 and 72 hours for conjunctival redness and chemosis were both 0.0 for all animals. At the 1 hour observation slight conjuctival redness was seen in one animal which resolved by the 24 hour observation. TEST GUIDELINES: US EPA OPPTS 870.2400; OECD No 405 (1987); 92/69/EEC B.5 (1992). REFERENCE SOURCE: L.M. Boczon, 2000. Primary eye irritation study in albino rabbits with AC375839 500 g/L SC(RLF 12360) BASF (unpublished) DocID 2000/7000139. RELIABILITY (KLIMISCH SCORE): 1	SPECIES: Rabbits STRAIN: New Zealand White NO. OF ANIMALS/GROUP: 3 (male) TEST SUBSTANCE: AC375839 500 g/L SC(RLF 12360) RESULT: Negative REMARKS: The individual mean scores at 24, 48 and 72 hours for both erythema and oedema were 0.0 for all rabbits. TEST GUIDELINES: US EPA OPPTS 870.2500; OECD No 404 (1992); 92/69/EEC B.4 (1992). REFERENCE SOURCE: L.M. Boczon, 2000. Primary dermal irritation study in albino rabbits with AC375839 500 g/L SC(RLF 12360) BASF (unpublished) DocID 2000/7000138. RELIABILITY (KLIMISCH SCORE): 1
Conclusion on Classification: No classification	***Conclusion on Classification: No classification***

SENSITISATION

Respiratory sensitization	**Contact sensitization**
No formulation data provided.	SPECIES: Guinea pigs STRAIN: Albino Crl: (HA) BR NUMBER OF ANIMALS/GROUP: 20 (test) and 10 (naïve controls) (male animals only) TEST SUBSTANCE: AC375839 500 g/L SC(RLF 12360). Undiluted for both induction and challenge.

	RESULT: Negative REMARKS: No skin reactions were detected either during preliminary testing, or during the 9 induction applications of the undiluted material. No reactions were seen at the challenge test either in the treatment animals or in the naïve controls. TEST GUIDELINES: US EPA OPPTS 870.2600 (1998); OECD No 406 (1992); 92/69/EEC B.1; Japanese MAFF 59 NohSan No 4200, 1985, Dermal sensitization. REFERENCE SOURCE: S.M Glaza, 2000. Dermal sensitization study of AC375839 500 g/L SC(RLF 12360) in guinea pigs BASF (unpublished) DocID 2000/7000147. RELIABILITY (KLIMISCH SCORE): 1
Conclusion on classification: Insufficient data	***Conclusion on Classification: No classification***
Dermal absorption study	
TYPE OF STUDY: Dermal absorption in rats SPECIES: Rat STRAIN: NO.ANIMALS/SEX/GROUP: 4 TEST SUBSTANCE: ^{14}C-BAS 560F as the formulated product (BAS560 02 F, also known as "BAS 560F 500 g/l SC") and a 1/2000 dilution thereof (representative of the ready to use spray concentration). DOSE LEVELS: 5.0 mg/cm^2 and 0.0025 mg/cm^2. These corresponded to approximately 180 and 0.1 mg/kg bw (of the active ingredient). All rats were exposed for 10 hours, but they were sacrificed after 10, 24 or 168 hours after the commencement of treatment. ROUTE: Dermal GLP: Yes TEST GUIDELINES: OECD Draft guideline "Percutaneous Absorption: *in vivo* method (2000). EPA OPPTS 870.7600 (1998). REMARKS: The mean recoveries of radioactivity from all dose groups were in the range 96.11 – 108.83% of the total administered. The largest proportion of the radioactivity we recovered from the skin wash. (Note that the 10 hour sacrifice group had a single skin wash, but the other groups had a skin wash at the end of their exposure and a 2nd skin wash at sacrifice.) The relative amount of radioactivity absorbed (including excreta, cage wash, tissues/organs and carcass) increased with sacrifice time but decreased with increasing dose. The overall conclusion was that for the formulation concentrate, the maximum relative absorption was about 1.15%. For the aqueous dilution the maximum relative absorption was about 18.72%. REFERENCE SOURCE: Leibold, E and van Ravenzwaay, 2001. C14 BAS 560F Study of dermal absorption in rats. Study T-1085 (BN/425/005) BASF DocID 2002/10004701 RELIABILITY (KLIMISCH SCORE): 1	

Class 9 Ecotoxicity and environmental fate

Sub-class 9.1 Aquatic ecotoxicity, fate and degradation

Classification under this sub-class requires consideration of the acute and chronic aquatic toxicity of the substance and the bioaccumulative and persistence properties of the components of the substance.

Aquatic fate and degradation of metrafenone and its metabolites

Information on aquatic fate and degradation is summarised in Table A2.7.

Table A2.7: Summary of aquatic fate and degradation of metrafenone (BAS 560F).

Study type	Test results Metrafenone	Test method [reference number]
Abiotic degradation		
Hydrolysis	pH 4: Stable (50°C) pH 7: Stable (50°C) pH 9: Stable (50°C)	An, 1999 Study No. ENV 98-030 OECD 111 GLP Klimisch score:1
Photolysis Phosphate buffer pH 7	DT_{50}: 3.1 days (continual irradiation) DT_{90}: 10.2 days (continual irradiation) Environmental half-lives calculated using GC SOLAR* (30 cm body of water) Summer Latitude 40 DT_{50}: 12.3 days Winter Latitude 40 DT_{50}: 53.3 days	Fung, 2002 Study No. ENV 01-053 USEPA N 161-2 SETAC Part 1 (10) GLP Klimisch score:1
Natural Water pH 7.7	DT_{50}: 2.6 days (continual irradiation) DT_{90}: 8.5 days (continual irradiation) *GC SOLAR is a computer model developed by the USEPA.	Huang, 2002 Study No. ENV 01-050 USEPA N 161-2 SETAC Part 1 (10) GLP Klimisch score:1
Biodegradation (laboratory)		
Sturm test	0.13% relative CO_2 production observed at study termination (Day 28). Not considered rapidly biodegradable.	Bradley & Yan, 1999 Study No. ENV 98-031 OECD 301B GLP Klimisch score: 1
Dissipation (field)		
	River water 17°C, pH 7.9, DO 8.6 mg/L (time of collection) River sediment Loam, pH 8.0 OC% 2.6	Yan, 2001 Study No. ENV 00-014 SETAC Part 1, 8.2

<table>
<tr><th rowspan="2">Study type</th><th>Test results</th><th rowspan="2">Test method
[reference number]</th></tr>
<tr><th>Metrafenone</th></tr>
<tr><td></td><td>Pond water
23°C, pH 8.4, DO 11.0 mg/L (time of collection)
Pond sediment
Loam, pH 7.7 OC% 0.5

<table><tr><th>System</th><th colspan="2">Water</th><th colspan="2">Sediment</th><th colspan="2">Total System</th></tr><tr><td></td><td>DT_{50}</td><td>DT_{90}</td><td>DT_{50}</td><td>DT_{90}</td><td>DT_{50}</td><td>DT_{90}</td></tr><tr><td>River</td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>*Bromo</td><td>3.0</td><td>10.1</td><td>3.5</td><td>11.5</td><td>8.5</td><td>28.1</td></tr><tr><td>Tri</td><td>3.3</td><td>11.0</td><td>4.5</td><td>15.0</td><td>9.5</td><td>31.5</td></tr><tr><td>Pond</td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Bromo</td><td>4.4</td><td>14.7</td><td>3.9</td><td>13.0</td><td>9.2</td><td>30.5</td></tr><tr><td>Tri</td><td>4.7</td><td>15.6</td><td>4.3</td><td>14.4</td><td>10.0</td><td>33.1</td></tr></table>*
Bromo: Bromobenzyl ring ^{14}C radiolabelled BAS 560 F
Tri:Trimethoxy benzyl ring ^{14}C radiolabelled BAS 560 F

The maximum amount of metabolites listed:
CL 375816 8.5% at 100 days
CL 377160 6.5% at 14 days
CL377095 1.6% at 14 days
CL 377096 3.1% at 56 days
CL 375228 3.0% at 28 days
CL 4084564 1.7% at 100 days
Metabolite-1 (polar) 11.3% at 28 days (2-3 products)
Metabolite-2 1.8% at 100 days
Metabolite-3 2.2% at 100 days
Metabolite-4 3.2% at 56 days
Metabolite-5 5.0% at 14 days

BAS 560 F and metabolites will be degraded in water-sediment systems and will not persist in the aquatic environment.</td><td>OECD draft 1998
GLP
Klimisch score: 1</td></tr>
<tr><td colspan="3">Bioaccumulation</td></tr>
<tr><td>Bluegill sunfish
Lepomis macrochirus</td><td>Labels and concentration (µg/L) of BAS 560 F tested:
B) [bromophenyl-6-^{14}C] BAS 560 F: 4.4 (± 0.89)
C) [bromophenyl-6-^{14}C] BAS 560 F: 43 (± 7.5)
D) [trimethoxyphenyl-U-^{4}C] BAS 560 F: 4.5 (± 0.86)
E) [trimethoxyphenyl-U-^{4}C] BAS 560 F: 46 (± 8.8)

BCF
B) 470 C) 460 D) 490 E) 530

Most conservative value of 530 taken.

BAS 560 F is metabolized by bluegill sunfish resulting in a short half life of < 1 day. BAS 560 F is metabolised by)-demethylation of the trimethyloxyphenyl ring methoxyl groups to yield two isomeric desmethyl derivatives followed by glucuromide and possibly sulphate conjugation of these des-methyl metabolites.
Clearance time (CT_{50}): 0.53 d (most conservative value taken)
Clearance time (CT_{90}): 2.3 d (most conservative value taken)</td><td>Zulalian 2001
MET 01-001
OECD 305
OPPTS 850.1730
GLP
Klimisch score: 1</td></tr>
</table>

Conclusion
Metrafenone is considered bioaccumulative based on the results of the study in fish [BCF=530] and is considered not rapidly degradable.

Aquatic toxicity
The toxicity of metrafenone and Vivando to aquatic organisms is summarised in Table A2.8 and A2.8a.

Table A2.8: Summary of aquatic toxicity data for metrafenone and its metabolites.

Test species	Test type & duration	Test results[a, b]		Test method[c] [reference number]
		Active	Metabolites	
Fish				
Rainbow trout, *Oncorhynchus mykiss*	96 h Flow through	LC_{50} > 0.82 mg/L [measured] > 80% of [nominal]		Palmer et al. 1999 OECD CI USEPA Series 72 Study no. ECO 98-176 GLP Klimisch score: 1
	96 h Static		**Metabolite 4074484 (CL 375816)** Limit test LC_{50} > 100 mg/L [measured] > 95% of [nominal]	Zok, 2002 OECD 203 Study no. 12F0259/015085 GLP Klimisch score: 1
	96 h Static		**Metabolite 4074564** LC_{50} 16.4 mg/L [measured} [measured] > 80% of [nominal] at the start of experimentation, < 80% during experimentation (caused by problems with solubility).	Zok, 2002 OECD 203 Study no. 12F0321/015084 GLP Klimisch score: 1
Bluegill sunfish *Lepomis macrochirus*	96 h Flow through	LC_{50} > 0.87 mg/L [measured] > 80% of [nominal] *loading in one tank greater than guideline *QA/QC samples for water concentration < desired range.		Palmer et al. 1999 OECD CI USEPA Series 72 Study no. ECO 98-175 GLP Klimisch score: 1*
Fathead minnow	Early life stage	NOEC		Barker et al. 2000

Test species	Test type & duration	Test results[a, b]		Test method[c] [reference number]
		Active	Metabolites	
Pimephales promelas	test Exposure: 4 d pre-hatch 28 d post-hatch	0.228 mg/L (length and weight) LOEC 0.419 mg/L (length and weight) [measured] > 80% of [nominal]		OECD 210 USEPA Series 72-4a Study no. ETX-99-149 GLP Klimisch score: 1
Invertebrates				
Water flea ***Daphnia magna***	48 h Static	EC_{50} > 0.92 mg/L [measured] > 80% of [nominal]		Palmer et al. 1999 USEPA Series 72-2 OECD C2 Study no. ECO 98-174 GLP Klimisch score: 1
	21 d Static	NOEC 0.225 mg/L (Length) LOEC 0.462 mg/L (Length) [measured] < 80% prior to renewal therefore results based on [measured]		Barker et al. 2000 USEPA 72-4 Study no. ETX 99-148 GLP Klimisch score: 1
	48 h Static		**Metabolite 4074484 (CL 375816)** EC_{50} > 100 mg/L [measured] > 90% of [nominal]	Jatzek, 2002 OPPTS 850.1010 OECD 202 Study no. 2002/1004870 GLP Klimisch score: 1
	48 h Static		**Metabolite 4074564** EC_{50} 46 mg/L [measured] > 80% of [nominal] at the start of experimentation, < 80% during experimentation (caused by problems with solubility).	Jatzek, 2002 OPPTS 850.1010 OECD 202 Study no. 2002/1004869 GLP Klimisch score: 1
Midge ***Chironomus riparius***	40 d Static Water/sediment	EC_{50} > 1 mg/L NOEC > 1 mg/L LOEC		Krueger et al. 2001 ASTM/E 1383-93 BBA Guideline Study no. ETX-99-147 GLP Klimisch score: 2*

Test species	Test type & duration	Test results[a, b]		Test method[c] [reference number]
		Active	Metabolites	
		> 1 mg/L *Delay in emergence in the solvent control and other treatment groups lead to the study being extended from 28 to 40 days. Day 40 represented two consecutive days of no emergence in any of the treatment groups.		
Algae/Aquatic plants				
Green Alga ***Selenastrum capricornutum***	72 h Static	E_rC_{50} > 0.87 mg/L E_bC_{50} 0.711 mg/L %95 CI: 0.644 – 0.770 mg/L [measured] > 80% of [nominal] at the start of experimentation, < 80% at the end of experimentation (caused by problems with solubility).		Barker et al. 2000 OECD 201 Study no. ETX 99-146 GLP Klimisch score: 1
			Metabolite 4074484 (CL 375816) E_rC_{50} > 100 mg/L E_bC_{50} > 100 mg/L [measured] > 80% of [nominal]	Jatzek, 2002 OPPTS 850.5400 OECD 201 Study no. 2002/1004873 GLP Klimisch score: 1
			Metabolite 4074564 E_rC_{50} 38.7 mg/L 95% CI: ND E_bC_{50} 27.8 mg/L 95% CI: ND [measured] [measured] > 80% of [nominal] at the start of experimentation, < 80% during experimentation (solubility).	Jatzek, 2002 OPPTS 850.5400 OECD 201 Study no. 2002/1004872 GLP Klimisch score: 1

[a] Results are reported on the basis of nominal concentrations except where otherwise stated, Standard test guidelines provide for reporting of results on a nominal basis where measurements indicate the test substance remains within 20% of nominal.
[b] 95% confidence intervals are stated where available
[c] Unless otherwise stated, the tests were conducted according to the test method identified

Conclusion
Based on these data metrafenone does not trigger the threshold for toxicity in the aquatic environment, other than as a 9.1D biocide.

Table A2.8A: Summary of aquatic toxicity data for Vivando.

Test species	Test type & duration	Test results[a, b]	Test method[c] [reference number]
Fish			
Rainbow trout, *Oncorhynchus mykiss*	96 h Static	LC_{50} > 104 mg formulation/L [measured] [measured] < 80% of [nominal] day 4	Palmer et al. 2001 OECD C1 USEPA 72-1 Study no. ETX-00-305 GLP Klimisch score: 1
Invertebrates			
Water flea *Daphnia magna*	48 h Static	EC_{50} > 1.979 mg formulation/L [measured] NOEC 0.855 mg formulation/L [measured] (mortality) [measured] < 80% of [nominal] day 2	Drottar et al. 2001 OECD C2 USEPA 72-2 Study no. ETX-99-248 GLP Klimisch score: 1
Algae/ Aquatic plants			
Green Alga *Selenastrum capricornutum*	72 h Static	E_rC_{50} > 2.248 mg formulation/L [measured] E_bC_{50} > 2.248 mg formulation/L [measured] NOEC 0.294 mg formulation/L [measured] [measured] < 80% of [nominal] day 2	Barker et al. 2000 OECD 201 Study no. ETX-99-249 GLP Klimisch score: 1

Conclusion
Based on these data Vivando does not trigger the threshold for toxicity in the aquatic environment, other than as a 9.1D biocide.

Sub-class 9.2 Soil ecotoxicity and terrestrial fate

Classification under this sub-class requires consideration of the persistence of the components of Vivando in soil, and the toxicity of Vivando to soil-dwelling invertebrates (e.g. earthworm), soil microbial function and terrestrial plants resulting from soil based exposure.

Data on the adsorption, mobility and field dissipation of the active ingredient is used in the ecological risk assessment for the substance (refer to Appendix 3).

Terrestrial fate and degradation of metrafenone and Vivando

Information on terrestrial fate and degradation is summarised in Tables A2.9 and A2.9A.

Table A2.9: Terrestrial fate and degradation of metrafenone and its metabolite.

Test type	Test results		Test method[a] [reference number]
	Metrafenone	Metabolites	
Abiotic degradation Photolysis	Silty loam soil pH 7.5, % OC 2.03, 20°C DT_{50}: 15.5 days (continuous radiation) (1^{st} order kinetics) (12 h light/dark cycle) DT_{50}: 31 days Major degradation product: CL 377160 19% after 14 days 6.4% after 30 days DT_{50}: 6 days (continuous radiation) (12 h light/dark cycle) DT_{50}: 12 days		Ta, 2001 SETAC section 2 Study No. ENV 00-004 GLP Klimisch score: 1
Biodegradation (Laboratory) Aerobic	Silty loam soil pH 7.5, % OC 2.03, 20°C DT_{50}: 257 days DT_{90}: 850 days (1^{st} order kinetics)		Steinfuhrer, 2000 SETAC section 1.1 Study No. CFS 1999-080 GLP Klimisch score: 1
	Loamy sand pH 6.2, % OC 0.63, 20°C DT_{50}: 182 days DT_{90}: 606 days (1^{st} order kinetics) Sandy loam pH 7.1, % OC 1.02, 20°C DT_{50}: 365 days DT_{90}: 1212 days (1^{st} order kinetics) Clay loam pH 7.3, % OC 0.96, 20°C DT_{50}: 289 days DT_{90}: 959 days (1^{st} order kinetics)		Steinfuhrer, 2000 SETAC section 1.1 Study No. CFS 1999-078 GLP Klimisch score: 1
		CL 377160 Silty Clay loam pH 7.9, OC% 1.3, 20°C DT_{50}: < 7 days Loamy sand pH 7.2, OC% 1.1, 20°C	Afzal, 2002 SETAC, section 1.1 Study No. 92517 GLP Klimisch score: 1

		DT_{50}: < 7 days Sandy loam pH 8.7, OC% 2.0, 20°C DT_{50}: < 7 days	
	Loamy sand pH 6.3, % OC 0.72, 10°C DT_{50}: 693 days DT_{90}: 2303 days (1^{st} order kinetics)		Steinfuhrer & Weis, 2000 SETAC section 1.1 Study No. 1999-079 GLP Klimisch score: 1
Biodegradation (Laboratory) Anaerobic	Silt loam soil pH 7.2, %OC 2.22, 20°C DT_{50}: 8 days DT_{90}: 27 days		van Dijk & Kunz, 2001 SETAC, section 1.2 Study No. ENV01-001 GLP Klimisch score: 1
	Silty clay loam soil pH 7.1, %OC 1.3, 20°C DT_{50}: 14.9 days DT_{90}: 49.4 days		Huang, 2002 SETAC, section 1.2 Study No. ENV01-001 GLP Klimisch score: 1
Soil Dissipation (Field)	Germany - Loamy sand BAS 560F 200 g as/L Application rate: 400 g as/ha DT_{50}: 144 days DT_{90}: 478 days (simple first order kinetics) (r^2 = 0.89) DT_{50}: 124 days DT_{90}: 637 days (biphasic first order kinetics) (r^2 = 0.91)		Jones, 2002 SETAC, 1995 Study no. 4701 GLP Klimisch score: 1
	UK – Sandy clay loam BAS 560F 200 g as/L Application rate: 400 g as/ha DT_{50}: 149 days DT_{90}: 495 days (simple first order kinetics) (r^2 = 0.42)		Smalley, 2002 SETAC, 1995 Study no. 4796 GLP Klimisch score: 1
	Denmark - loam BAS 560F 200 g as/L Application rate: 400 g as/ha DT_{50}: 221 days DT_{90}: 734 days (simple first order kinetics) (r^2 = 0.55) DT_{50}: 54 days DT_{90}: >1000 days (biphasic first order kinetics) (r^2 = 0.94)		Bramber, 2002 SETAC, 1995 Study no. OAT6 GLP Klimisch score: 1
	Northern France - Silt BAS 560F 200 g as/L Application rate: 400 g as/ha DT_{50}: 70 days		Bramber, 2002 SETAC, 1995 Study no. OAT10 GLP

	DT_{90}: 233 days (simple first order kinetics) (r^2 = 0.74) DT_{50}: 31.6 days DT_{90}: 493 days (biphasic first order kinetics) (r^2 = 0.80)			Klimisch score: 1
Soil accumulation	See Table A2.9A			
Adsorption/desorption	Metrafenone			
	Soil	Kd	Koc	Fang, 2001 OECD 106 Study No. ENV00-02701 GLP Klimisch score: 1
	Sandy loam pH 5.8 %OC 4.65	615	5556	
	Sandy loam pH 5.9 %OC 2.29	110	3794	
	Silt loam pH 7.4 %OC 2.27	49.4	1592	
	Loam pH 7.6 %OC 1.33	38.4	2367	
	Silt loam pH 5.9 %OC 1.09	35.9	2214	
Adsorption/desorption	**Metabolite CL 377160**			
	Soil	Kdes, f	Koc	Volkel, 2002 OECD 106 Study No. EXA 01 045 GLP Klimisch score: 1
	Loam pH 4 – 5.5, %OC 3 - 4	652.8	21649	
	Clay loam pH >7.5, %OC < 0.5 - 1	172.7	2465	
	Silt loam pH 5.5 – 7.0, %OC 1.5 – 3.0	116.5	3459	
	Silty clay loam pH 5.5 - >7.5, %OC 1.5 – 5	117.7	2199	
	loamy sand pH < 4.5, %OC > 10	138.0	2722	

[a] unless otherwise stated, the tests were conducted in accordance with the named test guideline

Conclusion

Metrafenone exhibited high persistence in soil under aerobic conditions, with field and laboratory half lives exceeding 100 days. Soil photolysis and anaerobic degradation are relatively rapid by comparison (DT_{50} < 20 days). Based on the sorption studies metrafenone is not expected to be mobile in soil, therefore no leaching studies were submitted.

Based on these data metrafenone is considered not to meet the HSNO criteria for degradability in soil < 30 days, i.e., it is not rapidly degradable.

Given these results the applicant has provided field studies to measure the accumulation in soil over time (summarised below).

Table A2.9A: Terrestrial fate and degradation of Vivando.

Test type	Test results Vivando	Test method[a] [reference number]
Soil accumulation **Italy 1999-2005**	Clay soil pH 8.0, %OC 1.2 Application rate: 8 x 100 g ai/ha Crop: Bare Soil Interval 14 days <u>First year (1999)</u> 0 – 10 cm layer 0.13 mg/kg following 8 applications <u>Second year (2000)</u> 0 – 10 cm layer 0.07 mg/kg prior to 1st application 0.23 mg/kg following 8 applications 10 – 20 cm layer 0.07 mg/kg following 8th application 0.06 mg/kg 175 days after 1st application of season 20 – 30 cm layer 0.04 mg/kg 175 days after 1st application of season <u>Third year (2001)</u> 0 – 10 cm layer 0.1 mg/kg prior to 1st application 0.16 mg/kg following 1st application 0.65 mg/kg following 8th application 10 – 30 cm layer < 0.02 mg/kg prior to 1st application 10 – 20 cm layer 0.04 mg/kg following 8th application <u>Fourth year (2002)</u> 0 – 10 cm layer 0.09 mg/kg prior to 1st application 0 – 5 cm layer 0.27 mg/kg following 1st application 0.43 mg/kg following 8th application 10 – 20 cm layer 0.03mg/kg prior to first application <u>Fifth year (2003)</u> 0 – 5 cm layer 0.31 mg/kg prior to 1st application 0.39 mg/kg following 1st application 0.57 mg/kg following 8th application 0.25 mg/kg 181 days following 8th application 5 – 10 cm layer	Johnston, 2002 SETAC 1995 Study No. BN-IT-99-310 GLP Klimisch score: 1

	0.03 – 0.06 mg/kg prior to 1st application 0.03 – 0.07 mg/kg range between 8th application and 181 days following 8th application 10 – 20 cm layer < 0.02 – 0.06 mg/kg prior to 1st application < 0.02 – 0.04 mg/kg range between 8th application and 181 days following 8th application 20 – 30 cm layer < 0.02 mg/kg prior to 1st application < 0.02 – 0.02 mg/kg range between 8th application and 181 days following 8th application No residues of the metabolite CL377160 were detected at or above the LOQ of 0.02 mg/kg in any of the treated specimens, which demonstrated that there was no significant accumulation of residues of CL 377160 in soil following six years of treatments with the parent compound according to the use pattern in grapevines. See Figure 2 for graphical representation of soil accumulation data.	
Soil accumulation **Spain 1999-2005**	Sandy loam pH8.4 , %OC 0.2 Application rate: 8 x 60 - 160 g ai/ha Crop: Soil Interval 14 days <u>First year (1999)</u> 0 – 10 cm layer 0.09 mg/kg following 8th application <u>Second year (2000)</u> 0 – 10 cm layer 0.03 mg/kg prior to first application 0.12 mg/kg following 8th application <u>Third year (2001)</u> 0 – 10 cm layer 0.08 mg/kg prior to first application 0.13 mg/kg following 8th application <u>Fourth year (2002)</u> 0 – 10 cm layer 0.07 mg/kg prior to first application 0.19 mg/kg following 8th application 0.07 mg/kg 181 days following 8th application <u>Fifth year (2003)</u> 0 – 5 cm layer 0.16 mg/kg prior to first application 0.33 mg/kg following 8th application 0.11 mg/kg 182 days following 8th application 5 – 10 cm <0.02 – 0.06 mg/kg range between 8th application and	Johnston, 2006 SETAC 1995 Study No. BN-SP-99-309 GLP Klimisch score: 1

	182 days following 8th application 10 – 20 cm <0.02 mg/kg between 8th application and 182 days following 8th application <u>Sixth year (2004)</u> 0 – 5 cm layer 0.14 mg/kg following 1st application 0.26 mg/kg following 8th application 0.07 mg/kg 188 days following 8th application 0.06 mg/kg 375 days following 8th application 5 – 10 cm layer < 0.02 – 0.02 mg/kg range between 8th application and 375 days following 8th application 10 – 20 cm layer < 0.02 mg/kg range between 8th application and 375 days following 8th application. No residues of metabolite CL 377160 were detected at or above the LOQ of 0.02 mg/kg in any of the treated specimens even after four years of applications of parent BAS 560 F according to the use pattern in grapevines. See Figure 3 for graphical representation of soil accumulation data.	
Soil accumulation Germany 1999-2005	Sandy silt loam pH 8.1, %OC 2.56 Crop: Grapes Application rate: 8 x 60 - 160 g ai/ha Interval 14 days <u>First year (1999)</u> 0 – 10 cm layer 0.162 mg/kg prior to 8th application 0.114 mg/kg prior to first application of 2000 10 – 20 cm layer No residues detected. <u>Second year (2000)</u> 0 – 10 cm layer 0.186 mg/kg prior to the 4th application 10 – 20 cm layer Residues 0.007 – 0.011 mg/kg before the 4th application and after the 8th application <u>Third year (2001)</u> 0 – 5 cm layer 0.297 mg/kg prior to the 1st application 0.390 mg/kg following the 8th application	Johnston, 2006 SETAC 1995 Study No. BN-GE-99-302 GLP Klimisch score: 1

	5 – 10 cm layer 0.037 – 0.068 mg/kg 10 – 20 cm layer 0.008 – 0.025 mg/kg 20-30 cm layer < 0.005 – 0.016 mg/kg <u>Fourth year (2002)</u> 0 – 5 cm layer 0.408 mg/kg following the 1st application 0.489 mg/kg prior to 8th application 0.411 mg/kg following 8th application <u>Fifth year (2003)</u> 0 – 5 cm layer 0.397 mg/kg prior to 1st application 5th year 0.345 mg/kg following 1st application 0.381 mg/kg following 8th application 5 – 10 cm layer 0.056 – 0.126 mg/kg 10 – 20 cm layer 0.009 – 0.040 mg/kg 20 – 30 cm layer < 0.005 – 0.013 mg/kg <u>Sixth year (2004)</u> 0 – 5 cm layer 0.496 mg/kg prior to 4th application 0.491 mg/kg following 4th application 0.336 mg/kg prior to 8th application 0.393 mg/kg following 8th application 5 – 10 cm layer 0.061 – 0.139 mg/kg 10 – 20 cm layer 0.009 – 0.041 mg/kg 20 – 30 cm layer 0.005 – 0.020 mg/kg <u>May (2005)</u> 0 – 5 cm layer 0.363 mg/kg (last application August 2004) No residues of the metabolite CL 377160 were detected at or above the LOQ of 0.005 mg/kg in any of	

	the treated specimens. See Figure 4 for graphical representation of soil accumulation data.	
Soil accumulation Germany 1999-2005	Silt loam pH 7.5, %OC 2.17 Crop: Barley/wheat Application rate: 2 x 200 g ai/ha Interval approximately 14 - 20 days 1999 0 – 10 cm layer 0.024 mg/kg following 2nd application No residues found in 10 – 20 cm layer (LOQ 0.005 mg/kg) 2000 Wheat straw harvested 64 days after second application 1.32 mg/kg (in straw) 2002 0 – 5 cm layer 0.026 mg/kg prior to fifth application 0.119 mg/kg following 5th application 0.150 mg/kg following 6th application 2003 0 – 5 cm layer 0.058 mg/kg prior to 5th application 0.330 mg/kg prior to 8th application 0.292 mg/kg 56 days after the 8th application 2005 0.067 mg/kg prior to 11th application 0.396 mg/kg following the 11th application 0.270 mg/kg prior to 12th application 0.311 mg/kg following the 12th application 0.189 mg/kg 65 days after the 12th application 5 – 10 cm layer ≤ 0.077 mg/kg 10 – 20 cm layer ≤ 0.013 mg/kg Residues of metabolite CL 377160 were not detected at or above the LOQ of 0.005 mg/kg in treated specimens with the following isolated exceptions: 0-5 cm soil layer 0.007 mg/kg at 71 DAT10 (after harvest) 0.005 mg/kg immediately before and after the 12th application. No quantifiable CL 377160 residues were found at depths below the 5 cm soil layer. See Figure 5 for graphical representation of soil accumulation data.	Johnston, 2006 SETAC 1995 Study No. BN-GE-99-303 GLP Klimisch score: 1

	Conclusion: Metrafenone is expected to accumulate in soil with continuous use. A plateau is expected to be reached after 6 - 10 years (EFSA 2006).	

Figure 2: BAS 560 F residues in soil following 8 applications per year to bare soil at 100g ai/ha/application, with a 14 day spray interval.

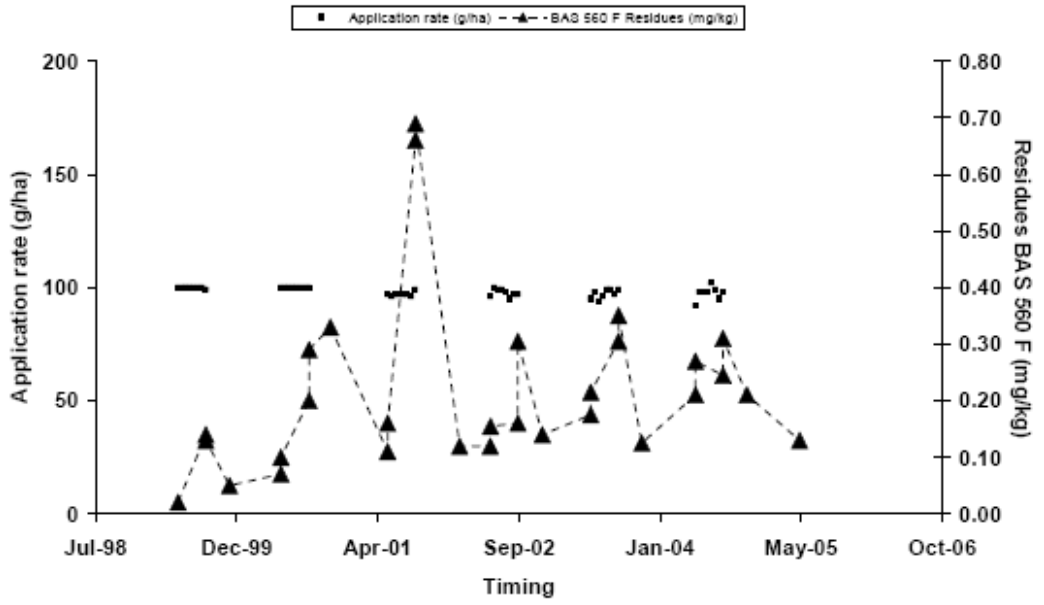


Figure 3: BAS 560 F residues in soil following 8 applications per year to bare soil at 100g ai/ha/application, with a 14 day spray interval.

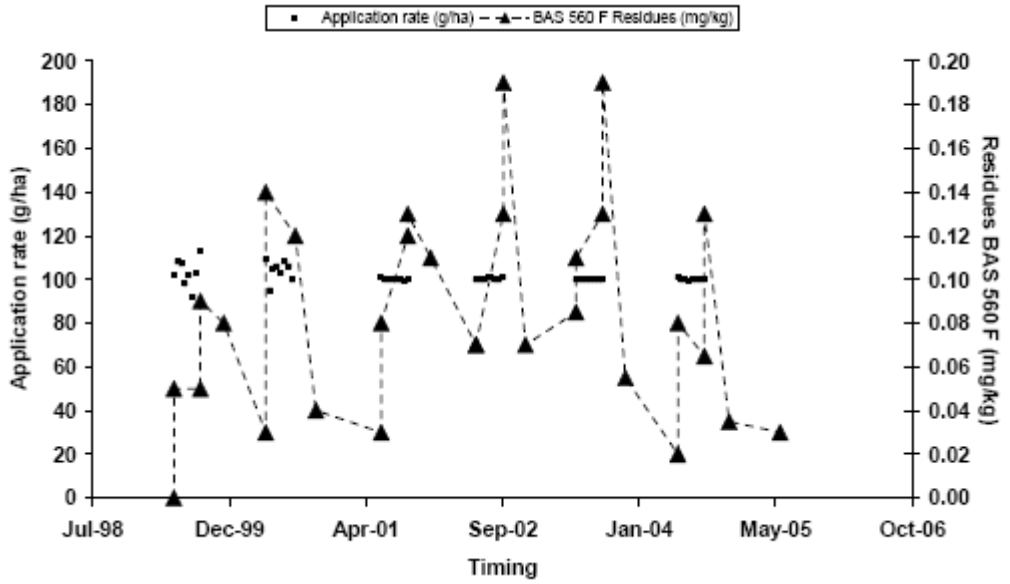


Figure 4: BAS 560 F residues in soil following 8 applications per year to grapes at 60 - 160g ai/ha/application, with a 14 day spray interval.

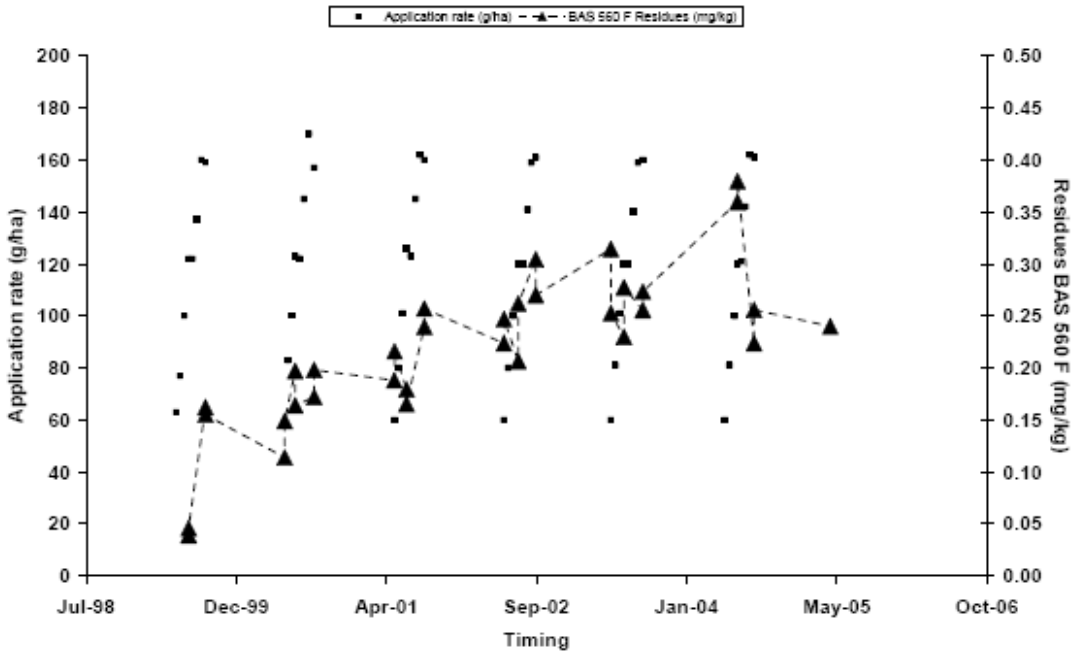
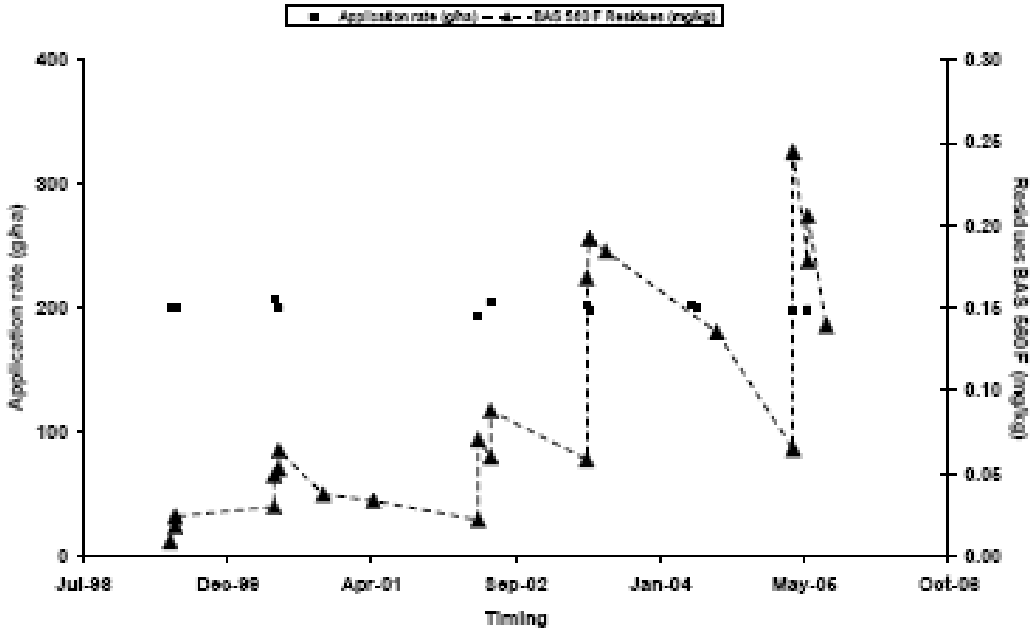


Figure 5: BAS 560 F residues in soil following 2 applications per year to cereals at 200g ai/ha/application, with a ^14day spray interval.



Soil toxicity

A summary of the toxicity of metrafenone and Vivando to soil dwelling macro-organisms, soil microbial function and terrestrial plants is provided in Table A2.10 and A2.10A.

Table A2.10: Summary of terrestrial toxicity data for metrafenone and the metabolite CL377160.

Test species	Test type & duration	Test results[a, b]		Test method[c] [reference number]
		Active	Metabolites	
Soil-dwelling invertebrates				
Earthworm ***Eisenia fetida***	Acute 14 d	Limit test LC_{50} > 1000 mg/kg soil *> 500 mg/kg soil* NOEC < 1000 mg/kg soil *> 500 mg/kg soil* (body weight)		Mulligan, 2001 OECD 207 Study no. ETX-99-151 GLP Klimisch score: 1
	Acute 14 d		**CL 377160** LC_{50} > 1000 mg/kg soil *> 500 mg/kg soil* NOEC > 1000 mg/kg soil *> 500 mg/kg soil*	Luhrs, 2001 OECD 207 Study no. 12141021 GLP Klimisch score:1
*Note: EFSA scientific report (2006) 58, 1-72. All earthworm values divided by a factor of 2 to allow for the greater amount of organic matter in test soil than in natural soil.				
Terrestrial plants				
Soil microbial function				
Activated sludge Respiration inhibition	3 h	EC_{50} > 600 mg/L The respiration rate of activated sludge was not adversely affected at a concentration of BAS 560 F equivalent to approximately 1.3x water solubility.		Hicks & Canez, 2002 OECD 209 Study no. EXA 01-044 GLP Klimisch score: 1
Carbon mineralisation	28 d		**CL377160** Soil type: Loamy sand pH 6.9, %OC 0.92 Application rate: 0.031 mg/kg dry soil (low) 0.31 mg/kg dry soil (high) Percent deviation from control: Low: -17% (<25%) High: 6% (<25%)	Barker, 2001 OECD 217 Study no. 84691/1 GLP Klimisch score: 1
Nitrogen transformation	28 d		**CL377160** Soil type: Loamy sand pH 6.9, %OC 0.92 Application rate: 0.031 mg/kg dry soil	Barker, 2001 OECD 217 Study no. 84691/2 GLP Klimisch score: 1

			(low) 0.31 mg/kg dry soil (high) Percent deviation from control: Low: -10% (<25%) High: -6% (<25%)	

[a] Results are reported on the basis of nominal concentrations except where otherwise stated, Standard test guidelines provide for reporting of results on a nominal basis where measurements indicate the test substance remains within 20% of nominal.
[b] 95% confidence intervals are stated where available
[c]Unless otherwise stated, the tests were conducted according to the test method identified

Conclusion

Based on the information (Table A2.10), neither metrafenone nor the metabolite CL377160 trigger the threshold for toxicity to the soil environment.

Table A2.10A: Summary of terrestrial toxicity data for Vivando.

Test species	Test type & duration	Test results[a, b]	Test method[c] [reference number]
Soil-dwelling invertebrates			
Earthworm ***Eisenia fetida***	8 weeks	LC_{50} > 4.0L/ha (8.0 mg ai/kg soil) NOEC ≥ 4.0L/ha (Adult mortality and biomass) NOEC ≥ 4.0L/ha (juvenile production)	Kreig, 2001 BBA VI, 2-2 (1994) Study no. 84723 GLP Klimisch score: 1
*Note: EFSA scientific report (2006) 58, 1-72. EFSA values LC_{50} and NOECs all > 10.44 mg ai/kg soil All earthworm values divided by a factor of 2 to allow for the greater amount of organic matter in test soil than in natural soil.			
Terrestrial plants			
Seedling Emergence	21 d	The application of BAS 560 F 500 g/L SC caused no phytotoxic effects on the emergence or growth of any species (ten tested). Both application rates, 102 g ai/ha and 324 g ai/ha (measured), were therefore determined to be NOECs for all ten species.	Porch et al. 2001 OECD 208 OPPTS 850.4100 Study no. 85521 GLP Klimisch score: 1
Vegetative vigour (Risk assessment only)	21 d	The application of BAS 560 F 500 g/L SC caused no effect on plant condition, height, or weight on any species tested (ten tested). Both application rates, 108 g ai/ha and 320 g ai/ha (measured), were therefore determined to be NOECs for all ten species.	Porch & Krueger, 2001. OECD 208 OPPTS 850.4150 Study no. 85519 GLP Klimisch score: 1
Soil microbial function			
Carbon Mineralisation	28 d	Soil type: Sandy loam pH 6.4, %OC 1.1	Chapleo, 2001 OECD 216

<table>
<tr>
<td>Nitrogen Transformation</td>
<td>28 d</td>
<td>Application rate
0.150 kg ai/ha
1.5 kg ai/ha

Deviation from control:
0.150 kg ai/ha: 13.2% (< 25%)
1.5 kg ai/ha: 18.7% (< 25%)

Deviation from control:
0.150 kg ai/ha: -1.1% (< 25%)
1.5 kg ai/ha: 0.3% (< 25%)</td>
<td>OECD 217
Study no. ETX-00-240
GLP
Klimisch score: 1</td>
</tr>
<tr>
<td>Degradation of buried straw in litter bags</td>
<td>6 months</td>
<td>Application rate:
100 g ai/ha

Mean % degradation:
<table>
<tr><th></th><th>1 month</th><th>3 months</th><th>6 months</th></tr>
<tr><td>Control</td><td>36.850 (0.839)</td><td>60.197 (1.542)</td><td>65.686 (0.619)</td></tr>
<tr><td>BAS 560 02 F</td><td>36.953 (2.066)</td><td>56.270 (1.602)</td><td>65.490 (3.608)</td></tr>
<tr><td>Reference</td><td>36.327 (1.959)</td><td>61.620 (1.724)</td><td>69.634 (0.546)</td></tr>
</table>
<u>Conclusion</u>
BAS 560 02F did not adversely affect the rate of degradation of organic barley straw when compared with the water control.</td>
<td>Pease & Forster, 2002
Kula et al. 2000
Study no. 93577
GLP
Klimisch score: 1</td>
</tr>
</table>

[a] Results are reported on the basis of nominal concentrations except where otherwise stated, Standard test guidelines provide for reporting of results on a nominal basis where measurements indicate the test substance remains within 20% of nominal.
[b] 95% confidence intervals are stated where available
[c]Unless otherwise stated, the tests were conducted according to the test method identified

Conclusion

Based on the information (Table A2.10A), Vivando does not trigger the threshold for toxicity to the soil environment.

Sub-class 9.3 Terrestrial vertebrate ecotoxicity

The mammalian toxicity of metrafenone and Vivando has been addressed under sub-class 6. Key endpoints for both mammalian and avian toxicity are summarised in Table A2.11.

Table A2.11: Summary of terrestrial vertebrate toxicity data for metrafenone.

Test species	Test type & duration	Test results[a, b]	Test method[c] [reference number]
Mammals			
Rat			
Sprague-Dawley derived (Crl:CD(SD) BR)	Acute Oral	LD_{50}: > 5,000 mg/kg bw	Lowe, C.A. 1999. OECD 401 Study No. AC375839 GLP Klimisch score: 1
Sprague-Dawley derived. Crl:CD(SD)	Acute Dermal	LD_{50}: > 5000 mg/kg bw/day	Bradley, D. 1999. OECD 402 Study no. AC375839 GLP Klimisch score: 1
Birds			
Northern bobwhite *Colinus virginianus*	Acute oral	LD_{50} > 2025 mg ai/kg bw * environmental conditions outside guideline (relative humidity below)	Ahmed et al, 2000 OPPTS 850.2100 Study no. ETX-99-140 GLP Klimisch score: 1*
Mallard Duck *Anas platyrhynchos*	Acute oral	LD_{50} > 2025 mg ai/kg bw * environmental conditions outside guideline (relative humidity below)	Ahmed et al, 2000 OPPTS 850.2100 Study no. ETX-99-141 GLP Klimisch score: 1*
Northern bobwhite *Colinus virginianus*	Acute Dietary 5 days treatment 3 days recovery	NOEC 5314 mg ai/kg diet * environmental conditions outside guideline (relative humidity below)	Ahmed et al, 2000 OPPTS 850.2200 OECD 205 Study no. ETX-99-142 GLP Klimisch score: 1*
Duck *Anas platyrhynchos*	Acute Dietary 5 days treatment 3 days recovery	NOEC 5314 mg ai/kg diet *10 birds outside the recommended upper weight limit; * brooder unit conditions outside guideline; * environmental conditions outside guideline (relative humidity below); *food availability limited in treatment groups.	Ahmed et al, 2000 OPPTS 850.2200 OECD 205 Study no. ETX-99-143 GLP Klimisch score: 2*
Northern bobwhite *Colinus*		NOEC (number of eggs laid per hen) 1350 ppm	Rodgers & Ahmed, 2002 OPPTS 850.2300

virginianus		NOEL 126.26 mg ai/kg bw/day NOEC (mean eggshell thickness) 1350 ppm NOEL 119.5 mg ai/kg bw/day NOEC (proportion of fertile eggs per eggs set per hen or number viable embryos over number of eggs set) 1350 ppm NOEL 126.26 mg ai/kg bw/day NOEC (proportion of hatching per fertile eggs per hen or percent hatching of viable embryos) 1350 ppm NOEL 126.26 mg ai/kg bw/day (% of self hatched chicks, rel. to viab. 18-d Embryos) NOEC (proportion of 14-day old juveniles per number of hatchlings) 1350 ppm NOEL 119.5 mg ai/kg bw/day NOEC (14-day juvenile weights per hen) 1350 ppm NOEL 119.5 mg ai/kg bw/day	OECD 206 Study no. ETX-00-179 GLP Klimisch score: 1

[a] Results are reported on the basis of nominal concentrations except where otherwise stated, Standard test guidelines provide for reporting of results on a nominal basis where measurements indicate the test substance remains within 20% of nominal.
[b] 95% confidence intervals are stated where available
[c]Unless otherwise stated, the tests were conducted according to the test method identified

Conclusion

Based on the information (Table A2.11), metrafenone does not trigger the threshold for toxicity to terrestrial vertebrates as no effects were observed in any of the acute or chronic tests.

Sub-class 9.4 Terrestrial invertebrate ecotoxicity

A summary of the data on the toxicity of metrafenone and Vivando to honeybees and other non-target terrestrial invertebrates is provided in Table A2.12 and Table A2.12A.

Table A2.12: Summary of terrestrial invertebrate toxicity data for metrafenone.

Test species	Test type & duration	Test results[a, b]		Test method[c] [Reference number]
Honey bee ***Apis mellifera***	Oral 48 h Contact 48 h	LD_{50} > 114 µg/bee LD_{50} > 100 µg/bee		Strnad & Mulligan, 2002 OECD 213 OECD 214 Study no. ETX-99-150 GLP Klimisch score: 1

[a] Results are reported on the basis of nominal concentrations except where otherwise stated, Standard test guidelines provide for reporting of results on a nominal basis where measurements indicate the test substance remains within 20% of nominal.
[b] 95% confidence intervals are stated where available
[c]Unless otherwise stated, the tests were conducted according to the test method identified

Conclusion

Based on the information (Table A2.12), metrafenone does not trigger the threshold for toxicity to terrestrial invertebrates.

Table A2.12A: Summary of terrestrial invertebrate toxicity data for Vivando.

Test species	Test type & duration	Test results[a, b]	Test method[c] [Reference number]
Honey bee ***Apis mellifera***	Oral 48 h Contact 48 h	Limit tests LD_{50} > 119.2 µg formulation/bee NOEC 119.2 µg formulation/bee LD_{50} > 100 µg formulation/bee NOEC 100 µg formulation/bee	Strnad & Mulligan, 2002 OECD 213 OECD 214 Study no. ETX-99-152 GLP Klimisch score: 1

Conclusion

Based on the information (Table A2.12A), Vivando does not trigger the threshold for toxicity to terrestrial invertebrates.

Overall Conclusion - Classification

Metrafenone is classified as 9.1 D due to its biocidal nature.
Vivando is classified as 9.1 D due to its biocidal nature.

Table A2.13: Summary of ecotoxicity classifications for metrafenone and Vivando.

Sub-class	metrafenone	Vivando
9.1 Aquatic ecotoxicity	**9.1D Biocide**	**9.1D Biocide**

References

EFSA scientific report (2006) 58, 1-72. Metrafenone.

US Department of Health Human Services, 1997 Registry of Toxic Effects of Chemical Substances

APPENDIX 3: RISK ASSESSMENT

Introduction

Quantitative risk assessments have been carried out to evaluate the level of risk to operators, bystanders and the environment arising from the use of Vivando.

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 (see Appendix 6 for a description of the scales used for qualitative assessment).

Human health risk assessment

Assessment of risks to human health - manufacture

The applicant has indicated that manufacture of Vivando in New Zealand is unlikely to occur. However, as there is the possibility that Vivando could be manufactured in New Zealand in the future, the Agency has qualitatively assessed the risks of Vivando to human health and safety during manufacture and considers the risks to be ***negligible***.

This assessment is based on the following considerations:

- Quantitative assessment of the chronic risks to human health associated with exposure to Vivando during use indicated an acceptable level of risk even without the use of PPE. Workers involved in manufacture of Vivando will be required to comply with the requirements for PPE, as well as comply with DoL requirements for health and safety, and, therefore, the Agency considers the level of risk to workers to be ***negligible***.

- The Agency considers the risk of repeated exposure to bystanders during manufacture is sufficiently remote that it is not necessary to address, noting that members of the public are generally excluded from manufacturing facilities.

Assessment of risks to human health – importation, storage and transport

The Agency has qualitatively assessed the risk of Vivando to human health and safety during importation, transportation and storage and considers the risks to be ***negligible***.

This assessment is based on the following consideration:

- The Agency considers that the risk of carcinogenicity from Vivando during importation, transport or storage to be sufficiently remote that it is not necessary to address, given that exposure could only occur in isolated spillage incidents.

Assessment of risks to human health - disposal

The Agency has qualitatively assessed the risk to human health and safety during disposal of Vivando, and considers the risks to the health and safety of people during disposal of the substance to be ***negligible***.

This assessment is based on the following considerations:

- If Vivando is disposed of by means other than use, this will be in accordance with the requirements of the Hazardous Substances (Disposal) Regulations 2001 and the Resource Management Act 1991.

- The Agency notes that a quantitative assessment of the chronic risks to operators associated with exposure to Vivando during use indicated an acceptable level even if PPE was not used. This assessment includes the possibility of prolonged and repeated exposure to Vivando during use. The Agency considers it is even less likely that users or bystanders could be repeatedly exposed to Vivando during disposal to such an extent that carcinogenicity effects occur and therefore considers the chronic risk to human health during disposal of Vivando to be ***negligible***.

Assessment of risks to human health – use

Operator exposure assessment

The Agency 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 to metrafenone during the use of Vivando. 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 BBA model can use either the geometric mean or the 95th percentile model - the geometric mean was used for assessing Vivando. 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). Four different scenarios were modeled for Vivando as shown in Table A3.6.

The applicant states that the maximum application rate of Vivando is as follows:

- 0.3 L /ha (equivalent to 0.1545 kg a.i./ha).

The Agency has used this maximum application rate for conducting an operator exposure assessment. Table A3.1 details the estimated exposure for each scenario modeled. The following points have been taken into account for the purposes of calculating the estimated exposure. For each model only the conservative scenario as described below, has been addressed:

- the concentration of metrafenone in Vivando = 515 g/L
- 0.3 L of Vivando is applied per hectare
- the substance is sprayed using a tractor mounted/trailed broadcast air-assisted sprayer;
- a work rate of 8 hectares per day (the default value for orchard spraying used in the German BBA model) is used in the absence of specific work rate data in the New Zealand context;

- a 10% percutaneous absorption value was used (the default value for the German BBA model) in the absence of specific value for metrafenone; the applicant provided data on the proportion absorption in rat skin, these estimates being 1.15% for the concentrate and 18.7% for the diluted spray. These values were used by the applicant in their modeling, but the Agency did not consider these data should be used without comparative *in vitro* data between rat and human skin, and
- the bodyweight for operators is set at 70 kg.

Calculation of Acceptable Operator Exposure Level (AOEL)

The toxicological endpoint for assessment of occupational (worker) and bystander risks is the AOEL (Acceptable Operator Exposure Level). The AOEL is the maximum daily dose considered to be without adverse health effect for operators, workers and bystanders. It is based on the most appropriate NOAEL from relevant studies and is calculated by dividing the NOAEL by one or more uncertainty (safety) factors selected on the basis of the extent and quality of the available data, the species for which data are available and the nature of the effects observed.

$$\text{AOEL} = \frac{\text{NOEL (most relevant study)}}{\text{Safety Factors}}$$

Selection of NOEL:

The options for NOAEL were:

- The 24 month toxicity/oncogenicity study in male rats, NOAEL 24.9 mg/kg bw/day
- 2 generation reproductive toxicity in the rat, parental NOAEL 39 mg/kg bw/day.
- 13 week study in rats with 28 day recovery, from which the Agency established a NOAEL of 79 mg/kg bw/day
- 13 week supplementary study in rats from which the EU established a NOAEL of 43 mg/kg bw/day, that was used to derived the AOEL.

With respect to assigning an appropriate NOAEL to calculate the AOEL, the Agency has taken the likely duration and frequency of worker exposure into consideration. Despite the difficulties in the dataset associated with dose selection, the Agency used the NOAEL of 43 mg/kg bw/day from the 13 week supplementary rat toxicity study detailed above, noting that this value was used to establish an AOEL by the EU.

In calculating the AOEL, the Agency has used a combined safety factor of 100 to account for intra- and interspecies variation. In the absence of specific oral absorption data for metrafenone, and based on the reported high absorption at low dose levels the Agency has assumed 100% oral absorption.

$$\textbf{AOEL} = 43\ \frac{\text{mg/kg bw/day x 1.0}}{100} = \textbf{0.43 mg/kg bw/day}.$$

(The applicant derived their AOEL based on the NOAEL of 87 mg/kg bw/day from the 13 week rat study, so the resulting value was 0.87 mg/kg bw/day. The agency notes that this used the same uncertainty factors and assumes 100% absorption.)

Estimation of operator risk assessment and calculation of Risk Quotients

Using the parameters listed above the German BBA model was used to estimate operator exposures and the RQ values estimated for each scenario as in Table A3.1.

To assess the risks to operators the Agency has divided the estimated exposure values as calculated from the exposure modeling by the AOEL to derive a risk quotient (RQ) for each exposure scenario modeled (Table A3.1).

$$RQ = \frac{\text{Estimated Operator (or Bystander) Exposure}}{\text{AOEL}}$$

A RQ > 1 indicates the likelihood of a risk to the operator (or bystander).

Table A3.1: Estimated exposure to metrafenone for 70 kg operator under four different exposure scenarios as predicted from the UK PSDs interpretation of the BBA Model

Exposure scenario	Estimated operator Exposure (mg/kg bw/day)	RQ value
No personal protective clothing and equipment (PPE) during mixing, loading and application	0.0249	0.058
Gloves only during mixing and loading	0.0207	0.048
Gloves only during application	0.0236	0.055
Full PPE during mixing, loading and application (excluding respirator)	0.0013	0.003

The Agency notes that in all exposure situations modeled, risks to operators are considered to be at acceptable levels (RQ < 1). The Agency 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 Agency notes that the HSNO PPE requirements are not prescriptive allowing users to select an appropriate level of PPE. (The applicant reached similar conclusions. The risks the applicant derived were lower due to use of lower dermal absorption values and the higher AOEL.)

The Agency has assigned the suspected (6.7B) classification to metrafenone and this also applies to Vivando, and considers comment on the significance on this is appropriate. The Agency notes that the tumours in rats and mice appear to be the result of metabolic activation and overload of the liver in rodents, and that it is likely there will be a threshold for these tumours. This is consistent with the substance not being mutagenic and not initiating foci of change in rat liver. The AOEL has been derived based on liver and blood clinical biochemistry effects from a 13 week study in rats which are considered to reflect the beginning of the relevant liver changes. The Agency considers that if there is a carcinogenicity risk in humans, it would be associated with very high and prolonged exposures. The Agency notes that the above exposure estimates indicate that the risk to operators is acceptable.

Since the exposure estimates for operators are acceptable even without protective equipment the risk to flaggers and reentry workers are considered acceptable, noting that these workers are not exposed during mixing/loading.

Public health exposure and risk assessment

The main potential source of exposure to the general public from Vivando (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 spraydrift. The results from the quantitative modeling of operator exposure indicate the risk to operators from Vivando is low even if PPE is not worn. The Agency notes that although any potential bystanders will not be wearing PPE, they will not be directly handling the substance. The Agency concludes that the risk to bystanders from the use of Vivando is acceptable.

Environmental exposure and risk assessment

Assessment of environmental risks - manufacture, importation, transport and storage

The Agency has qualitatively assessed the risks to the environment of Vivando during manufacture, importation, transportation and storage and considers the risks to be ***negligible.***

This assessment is based on the following considerations:

- The magnitude of adverse effects on the environment from a spillage during manufacture, importation, transport or storage are considered by the Agency to be ***minor***, as although the substance is harmful to the aquatic environment, any spill would involve small quantities which would lead to localised effects only.

- The Agency also considers such an event to be ***highly improbable*** given adherence to the HSNO controls (e.g. packaging, identification and emergency management) and the Land Transport Rule 45001, Civil Aviation Act 1990 and Maritime Transport Act 1994 (as applicable).

Assessment of environmental risks – disposal

The Agency has qualitatively assessed the risks to the environment of disposal of Vivando and considers the risks to be ***negligible***.

This assessment is based on the following considerations:

- Vivando will generally be disposed of by normal use as a fungicide.

- If Vivando is disposed of by means other than use, this will be in accordance with the requirements of the Hazardous Substances (Disposal) Regulations 2001 and the Resource Management Act 1991. The Agency considers the likelihood of adverse effects to the environment arising from disposal to be ***highly improbable*** and the magnitude of such effects ***minor***.

Assessment of environmental risks - use

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).

$$\text{Acute RQ} = \frac{EEC_{\text{short term}}}{LC_{50} \text{ or } EC_{50}} \qquad \text{Chronic RQ} = \frac{EEC_{\text{long term}}}{NOEC}$$

If the RQ exceeds a predefined level of concern, this suggests that it may be appropriate to refine the assessment or to apply the approved handler control
(AH) 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 AH control can then be removed on a selective basis.

Levels of concern (LOC) developed by the USEPA (Urban and Cook 1986) and adopted by ERMA New Zealand, to determine whether a substance poses an environmental risk are provided in Table A3.2.

Table A3.2: Levels of concern as adopted by ERMA 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
Chronic RQ≥	1	High chronic risk
Plants (aquatic and terrestrial)		
Acute RQ≥	1	High acute risk
Mammals and birds		
Acute dietary RQ≥	0.5	High acute risk
Acute oral dose [granular products] RQ≥	0.5	High acute risk
Chronic RQ≥	1	High chronic risk

Aquatic risk

Assessment of Expected Environmental Concentration
The Agency has used the Generic Estimated Environmental Concentration Model v2 (GENEEC2) surface water exposure model (USEPA 2001) to estimate the EEC of metrafenone in surface water which may potentially arise as a result of spray drift and surface runoff from the applicant's proposed New Zealand use pattern.

The parameters used in the GENEEC2 modeling are listed in Table A3.3 and represent the recommended use on pumpkin/winter squash (highest rate) as a conservative estimate.

Table A3.3: Input parameters for GENEEC2 analysis.

	Metrafenone	Reference
Application rate	154.5 g ai/ha	Product Label
Application frequency	2	Product Label
Application interval	14 days	Product Label
K_d	35.9*	Fang, 2001 Study No. ENV00-02701
Aerobic soil DT_{50}	327.15 days**	Steinfuhrer, 2000 Study No. CFS 1999-078/CFS 1999-080
Pesticide wetted in?	No	Product Label
Methods of application	Aerial Ground	Product Label does not stipulate, aerial and ground GENEEC defaults followed.
'No spray' zone	NA	

Water solubility	0.492 mg/L	Yan, 1998 Study No. ENV 98-010
Aerobic aquatic DT_{50}	10 days***	Yan, 2001 Study No. ENV 00-014
Aqueous photolysis DT_{50}	53.3 days Latitude 40° (Winter)	Fung, 2002 Study No. ENV 01-053

*The lowest of the K_d values measured in a non-sand textured soil (i.e. not sand, coarse sand, fine sand, loamy sand) (USEPA, 2001).
**The soil DT_{50} value of 327.15 for metrafenone follows the GENEEC2 calculation of the upper 90% confidence limit on the mean value ($n \geq 2$) of the five aerobic laboratory DT_{50} values (257, 365, 289, 182, 693 days) measured at 20°C (USEPA, 2001).
***Longest value taken in accordance with GENEEC2 guidance document (USEPA, 2001).

Output from the GENEEC2 model.
Aerial application – worst case scenario

```
RUN No.   1 FOR metrafenone      ON   pumpkin       * INPUT VALUES *
-----------------------------------------------------------------
RATE (#/AC)   No.APPS &   SOIL  SOLUBIL   APPL TYPE  NO-SPRAY INCORP
 ONE(MULT)    INTERVAL     Kd   (PPB )    (%DRIFT)   ZONE(FT)  (IN)
-----------------------------------------------------------------
.138(   .271)   2  14      35.9  492.0   AERL_B( 13.0)    .0    .0


FIELD AND STANDARD POND HALFLIFE VALUES (DAYS)
-----------------------------------------------------------------
METABOLIC  DAYS UNTIL  HYDROLYSIS   PHOTOLYSIS   METABOLIC  COMBINED
 (FIELD)   RAIN/RUNOFF   (POND)     (POND-EFF)    (POND)     (POND)
-----------------------------------------------------------------
 327.15        2          N/A     53.30- 6609.20    10.00      9.98


GENERIC EECs (IN MICROGRAMS/LITER (PPB))     Version 2.0 Aug 1, 2001
-----------------------------------------------------------------
    PEAK      MAX 4 DAY     MAX 21 DAY    MAX 60 DAY    MAX 90 DAY
    GEEC      AVG GEEC       AVG GEEC      AVG GEEC      AVG GEEC
-----------------------------------------------------------------
     3.21        3.03          2.14          1.14
```

The Estimated Environmental Concentration (EEC) for metrafenone as estimated by GENEEC2 are:
Peak EEC: 0.00321 mg/L
Chronic EEC (21 days): 0.00214 mg/L

Assessment of acute risk
No acute risk assessment was performed as no acute effects have been demonstrated.

Assessment of chronic risk
Table A3.4: Aquatic ecotoxicity endpoints to be used in risk assessment

Exposure	Species	LC_{50} or EC_{50} (mg formulation/L)	LC_{50} or EC_{50} (mg a.i./L)
Chronic	*Onchorynchus mykiss**		0.228
	*Daphnia magna**		0.225

Table A3.5: Chronic risk quotients derived from the GENEEC2 model and chronic aquatic toxicity data.

	21-day EEC from GENEEC2 (mg/L)	NOEC (mg/L)	RQ (Chronic) EEC/ NOEC
Fish	0.00214	0.228	< 0.01
Crustacea		0.225	< 0.01

When compared against the relevant chronic levels of concern (Table A3.2), the chronic RQs derived from the GENEEC2 modeling for metrafenone indicate the following:

For fish and crustacean: the chronic risk is low

Based on the chronic RQs for freshwater species, the Agency considers it is not appropriate to instate the approved handler controls for Vivando when it is used in a wide dispersive manner, or by a commercial contractor. However, the Agency considers that the application rate proposed by the applicant and used in the modeling should be set as a maximum application rate.

Terrestrial risk
No risk assessment was performed as no effects have been demonstrated on terrestrial species.

Avian Toxicity
No risk assessment was performed as no effects have been demonstrated on avian species.

Risk to Terrestrial Invertebrates (Bees)
No risk assessment was performed as no effects have been demonstrated on terrestrial invertebrate species (bees).

Risk to Beneficial Invertebrates

Table A3.6: Summary of effects of exposure to 500 g ai/L SC Formulated Product (Vivando) on beneficial invertebrates.

<table>
<tr><th>Test species</th><th>Results</th><th>Test method[c] [Reference number]</th></tr>
<tr><td>Predaceous mite Typhlodromus pyri</td><td>A Tier 1 laboratory study to estimate the LR_{50} of AC375839 in a 500 g/L SC formulation (RLF12360) on Typhlodromus pyri (Acarr: Phytosendae).

Formulated Product 500 g/L SC

Corrected Mortality (7 days):
<table>
<tr><td>Treatment (g ai/ha)</td><td>Mean % mortality</td><td>Corrected mortality</td></tr>
<tr><td>Control</td><td>13.3</td><td>NA</td></tr>
<tr><td>100</td><td>15.0</td><td>1.9</td></tr>
<tr><td>200</td><td>10.0</td><td>-3.8</td></tr>
<tr><td>300</td><td>8.3</td><td>-5.8</td></tr>
<tr><td>400</td><td>5.0</td><td>-9.6</td></tr>
</table></td><td>Walker, 2001 Study no. ETX-00-225 Overneer (1988) Louis & Ufer (1995) GLP Klimisch score: 1</td></tr>
</table>

<table>
<tr><th>Test species</th><th>Results</th><th>Test method[c] [Reference number]</th></tr>
<tr><td></td><td>
<table>
<tr><td>500</td><td>8.3</td><td>-5.8</td></tr>
<tr><td>Meothrin</td><td>96.7</td><td>96.2</td></tr>
</table>
Note: Trigger value = 40%.

Fecundity (Total mean number of eggs per female):
<table>
<tr><td>Treatment</td><td>Mean no. eggs per female 10 days after treatment</td><td>Mean no. eggs per female 12 days after treatment</td><td>Mean no. eggs per female 14 days after treatment</td><td>Total mean no. eggs per female</td></tr>
<tr><td>Control</td><td>1.2</td><td>1.6</td><td>1.5</td><td>4.3</td></tr>
<tr><td>400 g ai/ha</td><td>0.5</td><td>0.1</td><td>0.8</td><td>1.4*</td></tr>
<tr><td>500 g ai/ha</td><td>1.0</td><td>0.3</td><td>0.7</td><td>2.0*</td></tr>
</table>
*Following 14 days after treatment there was a significant reduction in fecundity at both treatment levels when compared to the control (at P≤0.05 in ANOVA and Tukey test).

Note: Vivando formulation is applied at 155 g ai/ha, 2 times per season.

Conclusion:
</td><td></td></tr>
<tr><td>Predaceous mite Typhlodromus pyri</td><td>
A field study to evaluate the effects of AC 375839 500 g/L against the predatory mite, Typhlodromus pyri, in grape vines.
Application rates:
10.0 g/hectolitre (0.01%) (hectolitre = 100 L)
12.5 g/hectolitre (0.0125%)

(80 – 400 mL formulated product/ha)

Effect (mortality) of AC375839 500 g/L and the toxic standard on predatory mites (values corrected according to Abbot, 1925).
<table>
<tr><td>Assessment after application no.</td><td>Rate 1 (low)</td><td>Rate 2 (high)</td><td>Toxic standard</td></tr>
<tr><td>1</td><td>-23</td><td>39</td><td>21</td></tr>
<tr><td>2</td><td>-32</td><td>3</td><td>33</td></tr>
<tr><td>4</td><td>16</td><td>28*</td><td>26*</td></tr>
<tr><td>6</td><td>1</td><td>6</td><td>44*</td></tr>
<tr><td>8</td><td>15</td><td>6</td><td>56*</td></tr>
<tr><td>8 + 4 weeks</td><td>5</td><td>27</td><td>63*</td></tr>
<tr><td>8 + 6 weeks</td><td>30</td><td>14</td><td>35</td></tr>
</table>
* significantly different to the control (Dunnett’s test, p=0.05).
Note: Trigger value = 40%.

Mean number of predatory mite eggs per leaf.
<table>
<tr><td>Assessment after application no.</td><td>Control</td><td>Rate 1 (low)</td><td>Rate 2 (high)</td><td>Toxic standard</td></tr>
<tr><td>0</td><td>3.45 (1.38)</td><td>2.62 (1.92)</td><td>2.83 (2.66)</td><td>3.20 (1.12)</td></tr>
<tr><td>1</td><td>0.80</td><td>0.90</td><td>0.28*</td><td>0.26*</td></tr>
</table>
</td><td>Muther, 2000
Study no. ETX-99-139
GLP
Klimisch score: 1</td></tr>
</table>

<table>
<tr><th>Test species</th><th>Results</th><th>Test method[c] [Reference number]</th></tr>
<tr><td></td><td>
<table>
<tr><td></td><td>(0.27)</td><td>(0.32)</td><td>(0.18)</td><td>(0.17)</td></tr>
<tr><td>2</td><td>1.35
(0.41)</td><td>2.06
(1.38)</td><td>1.19
(0.90)</td><td>0.78
(0.47)</td></tr>
<tr><td>4</td><td>2.42
(0.60)</td><td>2.07
(0.51)</td><td>1.44
(0.80)</td><td>1.05*
(0.72)</td></tr>
<tr><td>6</td><td>1.10
(0.34)</td><td>1.06
(0.34)</td><td>1.45
(0.53)</td><td>0.64
(0.33)</td></tr>
<tr><td>8</td><td>1.03
(0.63)</td><td>0.88
(0.23)</td><td>1.04
(0.52)</td><td>0.41
(0.11)</td></tr>
<tr><td>8 + 4 weeks</td><td>3.00
(1.15)</td><td>2.46
(0.81)</td><td>2.23
(1.24)</td><td>1.39
(0.46)</td></tr>
<tr><td>8 + 6 weeks</td><td>0.32
(0.12)</td><td>0.19
(0.26)</td><td>0.31
(0.33)</td><td>0.31
(0.25)</td></tr>
</table>
*Statistically significant different to the control (Dunnett test, p=0.05).

Mean number of spider mites per leaf.
<table>
<tr><th>Assessment after application no.</th><th>Control</th><th>Rate 1 (low)</th><th>Rate 2 (high)</th><th>Toxic standard</th></tr>
<tr><td>0</td><td>0.00
(0.00)</td><td>0.02
(0.04)</td><td>0.02
(0.04)</td><td></td></tr>
<tr><td>1</td><td>0.00
(0.00)</td><td>0.01
(0.02)</td><td>0.00
(0.00)</td><td>0.00
(0.00)</td></tr>
<tr><td>2</td><td>0.00
(0.00)</td><td>0.00
(0.00)</td><td>0.00
(0.00)</td><td>0.00
(0.00)</td></tr>
<tr><td>4</td><td>0.00
(0.00)</td><td>0.00
(0.00)</td><td>0.00
(0.00)</td><td>0.00
(0.00)</td></tr>
<tr><td>6</td><td>0.01
(0.02)</td><td>0.00
(0.00)</td><td>0.04
(0.04)</td><td>0.00
(0.00)</td></tr>
<tr><td>8</td><td>0.01
(0.02)</td><td>0.02
(0.02)</td><td>0.28*
(0.33)</td><td>0.02
(0.04)</td></tr>
<tr><td>8 + 4 weeks</td><td>0.02
(0.04)</td><td>0.03
(0.04)</td><td>0.10
(0.14)</td><td>0.03
(0.04)</td></tr>
<tr><td>8 + 6 weeks</td><td>0.00
(0.00)</td><td>0.01
(0.02)</td><td>0.17
(0.33)</td><td>0.07
(0.16)</td></tr>
</table>
*Statistically significant different to the control (Dunnett test, p=0.05).

Based on the results, AC375839 500 g/L SC should be considered as harmless (<40% effect) according to (Heimann-Detlefsen, 1991) to predatory mite populations if used as tested (8 applications, spray interval 12 ± 2 days, rate between 80 and 400 mL per ha).</td><td></td></tr>
<tr><td>Predaceous mite Typhlodromus pyri</td><td>Effects of AC 375839 500 g/L SC on predatory mites (Typhlodromus pyri),under typical vine culture conditions on grapes vines, Germany 2000.

Application rates:
0.02% x 8 applications
(between 80 and 330 mL formulated product/ha used)
Spray interval (10 – 16 d)

Mean number of predatory mites per 25 leaves in the test plots.
<table>
<tr><th>Assessment after application</th><th>Control</th><th>Treatment</th><th>Effect (Standardized for Abbott)</th><th>Effect (Standardized for H&T)</th></tr>
</table></td><td>Ipach, 2000
Study no. CYD11
BBA Part VI, 23-2.3.4
Blumel et al. 2000
GLP
Klimisch score: 1</td></tr>
</table>

<table>
<tr><th>Test species</th><th>Results</th><th>Test method[c] [Reference number]</th></tr>
<tr><td></td><td>
<table>
<tr><td>no.</td><td></td><td></td><td></td><td></td></tr>
<tr><td>0</td><td>485</td><td>422</td><td></td><td></td></tr>
<tr><td>1</td><td>933</td><td>811</td><td>13</td><td>0</td></tr>
<tr><td>2</td><td>599</td><td>547</td><td>9</td><td>-5</td></tr>
<tr><td>3</td><td>302</td><td>284</td><td>6</td><td>-8</td></tr>
<tr><td>4</td><td>353</td><td>328</td><td>7</td><td>-7</td></tr>
<tr><td>6</td><td>154</td><td>139</td><td>10</td><td>-4</td></tr>
<tr><td>7</td><td>173</td><td>215</td><td>-24</td><td>-43</td></tr>
<tr><td>8</td><td>209</td><td>202</td><td>3</td><td>-11</td></tr>
<tr><td>8 + 4 weeks</td><td>169</td><td>172</td><td>-2</td><td>-17</td></tr>
</table>
Note: Trigger value = 40%.

Based on the results, AC375839 500 g/L SC should be considered as harmless to predatory mite populations if used as tested (8 applications, spray interval 12 ± 2 days, rate concentration of 0.02%).
</td><td></td></tr>
<tr><td>Predaceous mite Typhlodromus pyri</td><td>Effects of “BAS 560 02 F” on predatory mites (Typhlodromus pyri) under typical vine culture conditions on grapes vines, Germany 2001.

Application rates:
0.02% x 8 applications
(between 120 and 320 mL formulated product/ha used)
Spray interval (10 – 16 d)

Mean number of predatory mites per 25 leaves in the test plots.
<table>
<tr><td>Assessment after application no.</td><td>Control</td><td>Treatment</td><td>Effect (Abbott)</td><td>Effect (H&T)</td></tr>
<tr><td>0</td><td>34.4</td><td>36.9</td><td>-</td><td>-</td></tr>
<tr><td>1</td><td>25.3</td><td>25.9</td><td>-2</td><td>5</td></tr>
<tr><td>2</td><td>17.9</td><td>17.5</td><td>2</td><td>9</td></tr>
<tr><td>3</td><td>15.4</td><td>15.2</td><td>2</td><td>8</td></tr>
<tr><td>5</td><td>7.7</td><td>7.4</td><td>3</td><td>10</td></tr>
<tr><td>7</td><td>4.3</td><td>3.7</td><td>13</td><td>19</td></tr>
<tr><td>8</td><td>4.6</td><td>4.1</td><td>10</td><td>16</td></tr>
<tr><td>8 + 4 weeks</td><td>2.3</td><td>2.2</td><td>4</td><td>10</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td></tr>
</table>
Based on these results, it can be concluded that 8 applications of BAS 560 02 F at a concentration of 0.02% (corresponding to a maximum of 320 g formulation/ha in 1600L water/ha) are harmless to field populations of predatory mites.
</td><td>Ipach, 2001
Study no. BAS68
BBA Part VI, 23-2.3.4
Blumel et al. 2000
GLP
Klimisch score: 1</td></tr>
<tr><td>Predaceous mite Typhlodromus pyri</td><td>Effects of “BAS 560 02 F” on predatory mites (Typhlodromus pyri) under typical vine culture conditions on grapes vines, Germany 2001.

Application rates:
0.02% x 8 applications
(between 120 and 320 mL formulated product/ha used)
Spray interval (10 – 15 d)

Mean number of predatory mites per 25 leaves in the test plots.
<table>
<tr><td>Assessment after application no.</td><td>Control</td><td>Treatment</td><td>Effect (Abbott)</td><td>Effect (H&T)</td></tr>
</table>
</td><td>Ipach, 2001
Study no. BAS69
BBA Part VI, 23-2.3.4
Blumel et al. 2000
GLP
Klimisch score: 1</td></tr>
</table>

<table>
<tr><th>Test species</th><th>Results</th><th>Test method[c] [Reference number]</th></tr>
<tr><td></td><td>
<table>
<tr><td>0</td><td>12.2</td><td>13.0</td><td>-</td><td>-</td></tr>
<tr><td>1</td><td>9.6</td><td>9.0</td><td>6</td><td>11</td></tr>
<tr><td>2</td><td>5.2</td><td>5.0</td><td>4</td><td>9</td></tr>
<tr><td>3</td><td>4.8</td><td>4.9</td><td>-1</td><td>5</td></tr>
<tr><td>5</td><td>2.9</td><td>3.0</td><td>-4</td><td>2</td></tr>
<tr><td>7</td><td>2.3</td><td>2.4</td><td>-3</td><td>2</td></tr>
<tr><td>8</td><td>3.1</td><td>3.2</td><td>-1</td><td>4</td></tr>
<tr><td>8 + 4 weeks</td><td>3.1</td><td>3.3</td><td>-6</td><td>0</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td></tr>
</table>

Based on these results, it can be concluded that 8 applications of BAS 560 02 F at a concentration of 0.02% (corresponding to a maximum of 320 g formulation/ha in 1600L water/ha) are harmless to field populations of predatory mites.
</td><td></td></tr>
<tr><td>Predaceous mite Kampimodromus aberrans</td><td>
Side-effects of AC375,839 500g/L SC (Benzofenone) towards predatory mite Kampimodromus aberrans (Oud.) in vineyard.
Note: Benzofenone was the previous name of metrafenone.
Country: Italy
Application rate: 20 g ai/ha
No of applications: Six

<table>
<tr><td>Assessment after application no.</td><td>Control</td><td>Treatment</td></tr>
<tr><td>0</td><td>6.9</td><td>6.73</td></tr>
<tr><td>1 + 10</td><td>2.93</td><td>3.56</td></tr>
<tr><td>2 + 10</td><td>2.94</td><td>3.23</td></tr>
<tr><td>3 + 10</td><td>6.13</td><td>4.89</td></tr>
<tr><td>4 + 10</td><td>4.67</td><td>5.27</td></tr>
<tr><td>5 + 10</td><td>5.76</td><td>5.54</td></tr>
<tr><td>6 + 10</td><td>7.07</td><td>7.36</td></tr>
<tr><td>6 + 20 d</td><td>5.21</td><td>4.34</td></tr>
</table>

The mean of metrafenone treated plots shows no negative side-effects towards this population of Kampimodromus aberrans.
</td><td>Gennari, 1999
IOBC/WPRS 1992/XV/3
IOBC/WPRS n.5.4.2
Study no. 10-9
GLP
Klimisch score: 2</td></tr>
<tr><td>Parasitic Wasp Aphidius rhopalosiphi</td><td>
A Tier 1 laboratory study to estimate the LR_{50} of AC375839 in a 500 g/L SC formulation (RLF12360) on Aphidius rhopalosiphi (Hymenoptera: Bracoudae).

Formulated Product 500 g/L SC

Corrected Mortality (2 days):
<table>
<tr><td>Treatment (g ai/ha)</td><td>Mean % mortality</td><td>Corrected mortality</td></tr>
<tr><td>Control</td><td>0</td><td>NA</td></tr>
<tr><td>10</td><td>0</td><td>0</td></tr>
<tr><td>50</td><td>7.4</td><td>7.4</td></tr>
<tr><td>75</td><td>0</td><td>0</td></tr>
<tr><td>100</td><td>3.3</td><td>3.3</td></tr>
<tr><td>150</td><td>46.7</td><td>46.7</td></tr>
</table>
</td><td>Walker, 2001
Study no. ETX-00-226
Mead-Briggs, 1992
GLP
Klimisch score: 1</td></tr>
</table>

<table>
<tr><th>Test species</th><th>Results</th><th>Test method[c] [Reference number]</th></tr>
<tr><td></td><td>
<table>
<tr><td>300</td><td>0</td><td>0</td></tr>
<tr><td>Dimethoate</td><td>53.3</td><td>53.3</td></tr>
</table>

Fecundity mean no. of mummies per female after 12 d:
<table>
<tr><td>Treatment</td><td>Mean no. of mummies per female</td></tr>
<tr><td>Control</td><td>5.3</td></tr>
<tr><td>100 g ai/ha</td><td>3.1</td></tr>
<tr><td>150 g ai/ha</td><td>5.0</td></tr>
<tr><td>300 g ai/ha</td><td>1.1*</td></tr>
</table>

* 12 days after treatment there was a significant reduction in fecundity at 300 g ai/ha when compared to the control (at P≤0.05 in ANOVA and Tukey test).

Note: Vivando formulation is applied at 155 g ai/ha, 2 times per season.</td><td></td></tr>
<tr><td>Carabid beetles
Poecilus cupreus</td><td>Effect of BAS 560 02F on the ground dwelling predator Poeclius cupreus (Coleoptera, Carabidae) in a laboratory trial.

<table>
<tr><td>Application rate</td><td>Mortality %</td><td>Corrected mortality %</td><td>Mean number of consumed pupae/beetle</td><td>Reduction of food consumption</td></tr>
<tr><td>Control</td><td>0</td><td>-</td><td>5.97</td><td>-</td></tr>
<tr><td>0.6 L/ha</td><td>0</td><td>0</td><td>5.84</td><td>2.2</td></tr>
</table>

Assessed as harmless to populations to Poeclius cupreus up to 0.6 L/ha in 400L water/ha.

Note: Vivando formulation is applied at 0.3L/ha, 2 times per season.</td><td>Buhler, 2002
Study no. 132832
Heimbach et al. 2000
GLP
Klimisch score: 1</td></tr>
<tr><td>Lacewing
Chrysoperla carnea</td><td>Effect of BAS 560 02F on the lacewing Chrysoperla carnea in a laboratory trial.

<table>
<tr><td>Rate (mL/ha)</td><td>Mortality %</td><td>Corrected Mortality %</td><td>Reproduction (eggs/female/day)</td><td>Hatching rate %</td></tr>
<tr><td>Control</td><td>4.0</td><td>NA</td><td>30.7</td><td>84.3</td></tr>
<tr><td>200</td><td>8.0</td><td>4.2</td><td>30.3</td><td>79.2</td></tr>
<tr><td>600</td><td>8.0</td><td>4.2</td><td>33.8</td><td>84.5</td></tr>
</table>

Assessed as harmless to populations to Chrysoperla carnea up to 0.6 L/ha in 200L water/ha.</td><td>Drexler, 2002
Study no. 2002/1004854
Vogt et al. 2000
GLP
Klimisch score: 1</td></tr>
</table>

Risk to Beneficial Insects

No risk assessment was performed as no effects have been demonstrated on terrestrial invertebrate species.

Summary and conclusions of the ecological risk assessment

Based on the risk assessment for the aquatic and terrestrial environment as set out above, no risks to any of the species groups examined have been identified.

References

EPPO 2001. Guideline on the test methods for evaluating the side-effects of plant protection products. No PP 1/170(3)

EPPO 2002. Environmental risk assessment scheme for plant protection products. Chapter 10 honeybees. EPPO Bulletin 33
http://archives.eppo.org/EPPOStandards/PP3_ERA/pp3-10(2).pdf

ERMA New Zealand 2008a. *User Guide to HSNO Thresholds and Classifications.* ERMA New Zealand, Wellington.

European Commission, Guidance Document on terrestrial ecotoxicology under Council Directive 91/414/EEC, SANCO/ 10329/2002 rev. 2 final, 17 October 2002.
http://ec.europa.eu/food/plant/protection/evaluation/guidance/wrkdoc09_en.pdf

Urban DJ, Cook, NJ 1986. *Hazard Evaluation Division Standard Evaluation Procedure: Ecological Risk Assessment*. EPA 540/9-85-001. United States Environmental Protection Agency Office of Pesticide Programs, Washington DC, USA.

USEPA 2001. Generic Estimated Environmental Concentration Model v2 (GENEEC2). United States Environmental Protection Agency Office of Pesticide Programs, Washington DC, USA http://www.epa.gov/oppefed1/models/water/index.htm#geneec2

APPENDIX 4: DISCUSSION ON CONTROLS

Based on the hazard classification as shown in Table 6.1, the set of associated controls has been identified. These default controls, expressed as control codes[10], are listed in Table A4.1.

Table A4.1: List of default controls for Vivando

Toxicity Controls	
T1	Limiting exposure to toxic substances through the setting of TELs
T2	Controlling exposure in places of work through the setting of WESs.
T4	Requirements for equipment used to handle substances
T5	Requirements for protective clothing and equipment
Ecotoxicity Controls	
E1	Limiting exposure to ecotoxic substances through the setting of EELs
E2	Restrictions on use of substances in application areas
E6	Requirements for equipment used to handle substances
Identification Controls	
I1	Identification requirements, duties of persons in charge, accessibility, comprehensibility, clarity and durability
I9	Secondary identifiers for all hazardous substances
I11	Secondary identifiers for ecotoxic substances
I16	Secondary identifiers for toxic substances
I17	Use of generic names
I18	Requirements for using concentration ranges
I19	Additional information requirements, including situations where substances are in multiple packaging
I21	General documentation requirements
I28	Specific documentation requirements for toxic substances
I29	Signage requirements
Packaging Controls	
P1	General packaging requirements
P3	Criteria that allow substances to be packaged to a standard not meeting Packing Group I, II or III criteria
PS4	Packaging requirements as specified in Schedule 4
Disposal Controls	
D4	Disposal requirements for toxic or corrosive substances
D5	Disposal requirements for ecotoxic substances
D6	Disposal requirements for packages
D7	Information requirements for manufacturers, importers and suppliers, and persons in charge
D8	Documentation requirements for manufacturers, importers and suppliers, and persons in charge
Emergency Management Controls	
EM1	Level 1 information requirements for suppliers and persons in charge
EM7	Information requirements for ecotoxic substances
EM8	Level 2 information requirements for suppliers and persons in charge
EM11	Level 3 emergency management requirements: duties of person in charge, emergency

[10] Control codes are those assigned by ERMA NZ to enable easy cross reference with the regulations. A detailed list of these codes is contained in the ERMA New Zealand User Guide to the Controls Regulations.

	response plans
EM12	Level 3 emergency management requirements: secondary containment
EM13	Level 3 emergency management requirements: signage
Tank Wagon and Transportable Containers Controls	
The Hazardous Substance (Tank Wagons and Transportable Containers) Regulations 2004 prescribe a number of controls relating to tank wagons and transportable containers.	

Those controls which require calculations, derivations or extended discussion are considered in the following sections.

Toxicity Controls

Setting of TELs (Control Code T1)

Tolerable Exposure Limits (TELs) are designed to limit the extent to which the general public is exposed to hazardous (toxic) substances. A TEL represents the maximum concentration of a substance legally allowable in a particular medium, and can be set as either a guideline value or an action level that should not be exceeded. For the purposes of setting TELs, an environmental medium is defined as air, water, soil or a surface that a hazardous substance may be deposited onto.

TELs are established from PDE (potential daily exposure) values, which are themselves established from ADE (acceptable daily exposure) values or reference doses (RfD) which are similar to ADE but are used to protect against a specific toxic effect of concern.

Human exposure may also occur through food or drinking water. Exposure through food is managed via the establishment of Maximum Residue Limits (MRLs) as set by the Minister of Food Safety on the advice of the New Zealand Food Safety Authority (NZFSA). Exposure through drinking water is managed via the establishment of Maximum Acceptable Values (MAVs) as set by the Ministry of Health. MRLs and MAVs are also established from ADE values.

Setting of PDEs

If an ADE or RfD value is set for a substance, or component of a substance, a PDE value for each relevant exposure route must also be set. A PDE is an amount of substance (mg/kg bodyweight/day), calculated in accordance with Regulation 23, that estimates the relative likelihood of particular exposures. A PDE for any single exposure route is a fraction of the ADE or RfD, and the sum of all PDE values from all possible exposures must be less than or equal to the ADE or RfD.

The main routes of exposure considered are ingestion (food, water, air, soil), inhalation (air) and skin contact (surface deposition, water, soil).

Setting of ADEs

An ADE is an amount of a hazardous substance (mg/kg bodyweight/day), that, given a lifetime of daily exposure, would be unlikely to result in adverse human health effects. An

RfD (reference dose) is a similar measure that can be used to protect against a specific toxic effect of concern.

Regulation 11(1) of the Hazardous Substances (Classes 6, 8 and 9) Controls Regulations 2001 determines when an ADE/RfD is required to be set:

> *(1) This regulation applies to a class 6 substance if-*
> *(a) it is likely to be present in-*
> *(i) 1 or more environmental media; or*
> *(ii) food; or*
> *(iii) other matter that might be ingested; AND*
> *(b) it is a substance to which a person is likely to be exposed on 1 or more occasions during the lifetime of the person; AND*
> *(c) exposure to the substance is likely to result in an appreciable toxic effect.*

If all three requirements of regulation 11(1) are met, then an ADE/RfD should be set for the relevant component(s), and PDE and TEL values subsequently established for each relevant exposure route.

There are no toxicity (Class 6) classifications of Vivando that trigger the need to consider setting a TEL. 6.7B.

Where a substance is a pesticides or veterinary medicines active ingredient that is new to New Zealand and it is intended for use on a food crop or animal, the Agency will propose an ADE regardless of whether the requirements of Regulation 11 are met as this information may be of use to NZFSA in setting MRLs.

Based on the outcome of the human health risk assessment, the Agency notes that Vivando does not contain any components that meet the requirements of Regulation 11(a)(c). Therefore, there is no requirement to set ADEs, PDEs or TELs. However, as Vivando is intended for use on food crops and contains metrafenone, a new active ingredient to New Zealand, an ADE and PDE_{food} value are calculated for this component which will enable the NZFSA to set MRLs is needed. However, no TEL values are proposed.

Provide details of ADE and PDE. On review of the relevant toxicology data, the Agency considers that an ADE of 0.25 mg/kg bw/day should be adopted for metrafenone. Based on this value, and considering the main ingestion exposure to metrafenone would be via food stuff (70%), drinking water (20%) and other non-foodstuffs (10%), the Agency proposes that PDE_{food} = 0.18 mg/kg bw/day and $PDE_{drinking\ water}$ = 0.05 mg/kg bw/day should be set for metrafenone.

Setting acute reference doses (ARfD) for substances containing New Active ingredients.

The Agency has agreed with the New Zealand Food Safety Authority that we will set an acute reference dose (ARfD), for new active ingredients, when this is considered appropriate. This will provide a basis for the NZ Food Safety Authority to assess shorter term food residues if this should be required. In the case of metrafenone the Agency notes that the EU has not set an ARfD, and the Agency does not propose that a value be set in New Zealand due to the low acute toxicity of the compound.

Setting of WES (Control Code T2)

Workplace exposure standards (WES) are designed to protect persons in the workplace from the adverse effects of toxic substances. A WES is an airborne concentration of a substance (expressed as mg substance/m^3 of air, or ppm in air), which must not be exceeded in a workplace and only applies to places of work (Regulation 29(2), Hazardous substances (Classes 6, 8 and 9 Controls) Regulations 2001).

Regulation 29(1) of the Hazardous Substances (Classes 6, 8 and 9 Controls) Regulations 2001 determines when a WES is required to be set. If all three of the requirements of this regulation are met then a WES is required to be set.

Regulation 29 states:

(*1*) *This regulation and regulation 30 apply to a* ***class 6*** *substance if,-*

- *(a) under the temperature and pressure the substance is to be used in, it can become airborne and disperse in air in the form of inspirable or respirable dust, mists, fumes, gases or vapours; AND*
- *(b) human exposure to the substance is primarily through the inhalation or dermal exposure routes; AND*
- *(c) the toxicological and industrial hygiene data available for the substance is sufficient to enable a standard to be set.*

When setting WES, the Authority must either adopt a value already proposed by the Department of Labour or already set under HSNO or derive a value by taking into account the matters described in Regulation 30(2) of the Hazardous Substances (Classes 6, 8 and 9 Controls) Regulations.

The Agency typically adopts WES values listed in the Workplace Exposure Standards (Effective from 2002) document (refer to the link below).
http://www.osh.govt.nz/order/catalogue/pdf/wes2002.pdf

The Agency notes that Department of Labour WES values/overseas WES have been set for component A but considers that these values should not be applied to Vivando due to their low concentration. No other Department of Labour WES/overseas WES values have been set for any other components of Vivando. This indicates that the conditions of Regulation 29(1)(C) are not met as the Agency is not aware of industrial hygiene data for Vivando that would enable a WES to be set for any of the constituent components. Therefore, no WES values are proposed for any components of Vivando at this time.

Ecotoxicity Controls

Setting of EELs (Control code E1)

Regulation 33 of the Hazardous Substances (Classes 6, 8 and 9 Controls) Regulations 2001 specify that an environmental exposure limit (EEL) may be set for a class 9 substance for one or more environmental media if organisms that live in that environment may be exposed to the substance. An EEL is the (maximum) concentration of a substance in an environmental medium that will present a negligible risk of adverse environmental effects to organisms (excluding humans) in non-target areas.

As specified by regulation 32, a default EEL of 0.1 µg/L water is set for any class 9.1 substance, and 1 µg/kg soil (dry weight) for any class 9.2 substance.

For the purposes of setting EELs, an environmental medium is defined as water, soil or sediment where these are in the natural environment, or a surface onto which a hazardous substance may be deposited.

An EEL can be established by one of three means:

- Applying the default EELs specified in regulation 32
- Adopting an established EEL as provided by regulation 35(a)
- Calculating an EEL from an assessment of available ecotoxicological data as provided by regulation 35(b).

The Hazardous Substances and New Organisms (Approvals and Enforcement) Act 2005 added a new section (s77B) to the HSNO Act, which, amongst other things provided the Authority with the ability to set EELs as guideline values, rather than the previous pass/fail values.

However, until the Agency has developed formal policy on the implementation of s77B, it proposes not to set EELs for any components of Vivando at this time. It is also proposed that the default EEL water and soil values be deleted until the policy has been established.

Setting of Application Rate (Control Code E2)

These regulations relate to the requirement to set an application rate for a class 9 substance that is to be sprayed or applied to an area of land (or air or water) and for which an EEL has been set.

Although no EEL has been set for Vivando, the Agency proposes setting the application rate of 154.5 g ai/ha (0.3 L formulation/ha), twice per season as the maximum application rate for Vivando. This rate was used in the ecological risk assessment.

<u>Other controls required as a result of the ecological risk assessment.</u>

This substance is not to be applied onto or into water.

Identification controls

Identification of Toxic Components on Labels/Documentation (SDS)

The Hazardous Substances (Identification) Regulations 2001 specify that certain toxic components are required to be specified on the product label and on SDS documentation.

Identification of toxic components on labels

Regulations 25(e) and 25(f) require that certain toxic components are required to be specified on the product label.

Regulation 25(e) states:

...a toxic substance must be identified by...

'information identifying, by its common or chemical name, every ingredient, that would, independently of any other ingredient, give the substance a hazard classification of 6.1A, 6.1B, 6.1C, 6.5, 6.6, 6.7, 6.8 or 6.9, and the concentration of that ingredient in the substance."

Regulation 25(f) states:

...a toxic substance must be identified by...

"information identifying (other than an ingredient referred to in paragraph (E)) that would, independently of any other ingredient, give the substance a hazard classification of 6.1D, and the concentration of the ingredient that would contribute the most to that classification."

Identification of toxic components on SDS

Regulation 39(5) of the Hazardous Substances (Identification) Regulations 2001, states that certain corrosive and toxic components are required to be specified on documentation.

Regulations 39(5) states:

"The requirements of regulation 19(f) or (as the case requires) regulation 25(e) apply to all documentation; but any ingredient required by that provision to be identified (other than an ingredient to which regulation 26 applies) must also be identified by any Chemical Abstract Services number allocated to it."

Concentration cut-offs for component identification

Consistent with the guidance provided by GHS, the Hazardous Substances Standing Committee (HSSC) agreed that the concentration cut-offs triggering the requirement for identification of components on labels and documentation are:

HSNO Classification	Cut-off for label (% w/w)	Cut-off for SDS (% w/w)
6.5A, 6.5B, 6.6A, 6.7A	0.1	0.1
6.6B	1	1

6.7B	1	0.1
6.8A, 6.8C	0.3	0.1
6.8B	3	0.1
6.9A, 6.9B	10	1

Vivando - Components requiring identification

Under these regulations, as determined by the HSSC (March 2006), the name and concentration of the following components need to be specified on the label and documentation:

Label	Documentation
Metrafenone	Metrafenone

APPENDIX 5: LIST OF PROPOSED CONTROLS FOR VIVANDO

Table A5.1: Proposed controls for Vivando – codes, regulations and variations.

Control Code[11]	Regulation [12]	Topic	Variations
Hazardous Substances (Classes 6, 8, and 9 Controls) Regulations 2001			
T1	11-27	Limiting exposure to toxic substances	The following ADE and PDEs are set for metrafenone: ADE = 0.25 mg/kg bw/day PDE_{food} = 0.18 mg/kg bw/day $PDE_{drinking\ water}$ = 0.05 mg/kg bw/day. No TEL values are proposed for Vivando at this time.
T2	29, 30	Controlling exposure in places of work	No WES values are set at this time
T4/E6	7	Requirements for equipment used to handle hazardous substances	Controls T4 and E6 are combined.
T5	8	Requirements for protective clothing and equipment	
E1	32-45	Limiting exposure to ecotoxic substances	No EEL values are set at this time and the default EELs are deleted.
E2	46-48	Restrictions on use within application area	As no EELs have been set, no application rate is required to be set under this control at this time. However, an application rate is set as an additional control under Section 77A. The maximum application rate for Vivando shall be 154.5 g a.i./ha, twice per season.
Hazardous Substances (Identification) Regulations 2001			
I1	6, 7, 32-35, 36 (1)-(7)	General identification requirements Regulation 6 – Identification duties of suppliers Regulation 7 – Identification duties of persons in charge	

[11] Note: The numbering system used in this column relates to the coding system used in the ERMA New Zealand Controls Matrix. This links the hazard classification categories to the regulatory controls triggered by each category. It is available from the ERMA New Zealand website www.ermanz.govt.nz/resources and is also contained in the ERMA New Zealand User Guide to the HSNO Control Regulations.
[12] These Regulations form the controls applicable to this substance. Refer to the cited Regulations for the formal specification, and for definitions and exemptions.

Control Code[11]	Regulation [12]	Topic	Variations
		Regulations 32 and 33 – Accessibility of information Regulations 34, 35, 36(1)-(7) – Comprehensibility, Clarity and Durability of information	
I9	18	Secondary identifiers for all hazardous substances	
I11	20	Secondary identifiers for ecotoxic substances	
I16	25	Secondary identifiers for toxic substances	
I17	26	Use of Generic Names	
I18	27	Use of Concentration Ranges	
I19	29-31	Alternative information in certain cases Regulation 29 – Substances in fixed bulk containers or bulk transport containers Regulation 30 – Substances in multiple packaging Regulation 31 – Alternative information when substances are imported	
I21	37-39, 47-50	Documentation required in places of work Regulation 37 – Documentation duties of suppliers Regulation 38 – Documentation duties of persons in charge of places of work Regulation 39 – General content requirements for documentation Regulation 47 – Information not included in approval Regulation 48 – Location and presentation requirements for documentation Regulation 49 – Documentation requirements for vehicles	

Control Code[11]	Regulation [12]	Topic	Variations
		Regulation 50 – Documentation to be supplied on request	
I28	46	Specific documentation requirements for toxic substances	
I29	51-52	Duties of persons in charge of places with respect to signage	
Hazardous Substances (Packaging) Regulations 2001			
P1	5, 6, 7 (1), 8	General packaging requirements Regulation 5 – Ability to retain contents Regulation 6 – Packaging markings Regulation 7(1) – Requirements when packing hazardous substance Regulation 8 – Compatibility Regulation 9A and 9B – Large Packaging	
P3	9	Packaging requirements for substances packed in limited quantities	
PS4	Schedule 4	This schedule describes the minimum packaging requirements that must be complied with when a substance is packaged in limited quantities	
Hazardous Substances (Disposal) Regulations 2001			
D4 D5	8 9	Disposal requirements for Vivando	Controls D4 and D5 are combined
D6	10	Disposal requirements for packages	
D7	11, 12	Disposal information requirements	
D8	13, 14	Disposal documentation requirements	
Hazardous Substances (Emergency Management) Regulations 2001			
EM1	6, 7, 9-11	Level 1 emergency management information: General requirements	
EM7	8(f)	Information requirements for ecotoxic substances	
EM8	12-16, 18-20	Level 2 emergency management documentation requirements	
EM11	25-34	Level 3 emergency management requirements – emergency response plans	

Control Code[11]	Regulation [12]	Topic	Variations
EM12	35-41	Level 3 emergency management requirements – secondary containment	The following subclauses shall be added after subclause (3) of regulation 36: *(4) For the purposes of this regulation, and regulations 37 to 40, where this substance is contained in pipework that is installed and operated so as to manage any loss of containment in the pipework it—* *(a) is not to be taken into account in determining whether a place is required to have a secondary containment system; and* *(b) is not required to be located in a secondary containment system.* *(5) In this clause, pipework—* *(a) means piping that—* *(i) is connected to a stationary container; and* *(ii) is used to transfer a hazardous substance into or out of the stationary container; and* *(b) includes a process pipeline or a transfer line.* The following subclauses shall be added after subclause (1) of regulation 37: *(2) If pooling substances that do not have class 1 to 5 hazard classifications are held in a place above ground in containers each of which has a capacity of 60 litres or less—* *(a) if the place's total pooling potential is less than 20,000 litres, the secondary containment system must have a capacity of at least 25% of that total pooling potential:* *(b) if the place's total pooling potential is 20,000 litres or*

Control Code[11]	Regulation [12]	Topic	Variations
			more, the secondary containment system must have a capacity of the greater of— *(i) 5% of the total pooling potential; or* *(ii) 5,000 litres.* *(3) Pooling substances to which subclause (2) applies must be segregated where appropriate to ensure that leakage of one substance may not adversely affect the container of another substance.* The following subclauses shall be added after subclause (1) of regulation 38: *(2) If pooling substances which do not have class 1 to 5 hazard classifications are held in a place above ground in containers 1 or more of which have a capacity of more than 60 litres but none of which have a capacity of more than 450 litres—* *(a) if the place's total pooling potential is less than 20,000 litres, the secondary containment system must have a capacity of either 25% of that total pooling potential or 110% of the capacity of the largest container, whichever is the greater:* *(b) if the place's total pooling potential is 20,000 litres or more, the secondary containment system must have a capacity of the greater of—* *(i) 5% of the total pooling potential; or* *(ii) 5,000 litres* *(3) Pooling substances to which subclause (2) applies must be segregated where appropriate to*

Control Code[11]	Regulation [12]	Topic	Variations
			ensure that the leakage of one substance may not adversely affect the container of another substance.
EM13	42	Level 3 emergency management requirements – signage	
Hazardous Substances (Tank Wagons and Transportable Containers) Regulations 2004			
Regulations 4 to 43 where applicable	The Hazardous Substances (Tank Wagons and Transportable Containers) Regulations 2004 prescribe a number of controls relating to tank wagons and transportable containers and must be complied with as relevant.		
Section 77A Additional Controls			
The controls relating to stationary container systems, as set out in Schedule 8 of the Hazardous Substances (Dangerous Goods and Scheduled Toxic Substances) Transfer Notice 2004 (Supplement to the New Zealand Gazette, 26 March 2004, No. 35, page 767), as amended, apply to this substance, notwithstanding clause 1(1) of that schedule.			
Addition of subclauses after subclause (3) of Regulation 36 of the Hazardous Substances (Emergency Management Controls) Regulations 2001 (control EM12).			
Addition of clauses after Regulation 37 of the Hazardous Substances (Emergency Management Controls) Regulations 2001 (control EM12).			
Addition of clauses after Regulation 38 of the Hazardous Substances (Emergency Management Controls) Regulations 2001 (control EM12).			
The maximum application rate for Vivando shall be 154.5 g a.i./ha, twice per season.			
Vivando shall not be applied onto or into water.			

APPENDIX 6: QUALITATIVE DESCRIPTORS FOR RISK/BENEFIT ASSESSMENT

This section describes how the Agency staff and the Authority address the qualitative assessment of risks, costs and benefits. Risks and benefits are assessed by estimating the magnitude and nature of the possible effects and the likelihood of their occurrence. For each effect, the combination of these two components determines the level of the risk associated with that effect, which is a two dimensional concept. Because of lack of data, risks are often presented as singular results. In reality, they are better represented by 'families' of data which link probability with different levels of outcome (magnitude).

The magnitude of effect is described in terms of the element that might be affected. The qualitative descriptors for magnitude of effect are surrogate measures that should be used to gauge the end effect or the 'what if' element. Tables 1 and 2 contain generic descriptors for magnitude of adverse and beneficial effect. These descriptors are examples only, and their generic nature means that it may be difficult to use them in some particular circumstances. They are included here to illustrate how qualitative tables may be used to represent levels of adverse and beneficial effect.

Table 1 Magnitude of adverse effect (risks and costs)

Descriptor	Examples of descriptions - ADVERSE
Minimal	Mild reversible short term adverse health effects to individuals in highly localised area Highly localised and contained environmental impact, affecting a few (less than ten) individuals members of communities of flora or fauna, no discernible ecosystem impact Local/regional short-term adverse economic effects on small organisations (businesses, individuals), temporary job losses No social disruption
Minor	Mild reversible short term adverse health effects to identified and isolated groups Localised and contained reversible environmental impact, some local plant or animal communities temporarily damaged, no discernible ecosystem impact or species damage Regional adverse economic effects on small organisations (businesses, individuals) lasting less than six months, temporary job losses Potential social disruption (community placed on alert)
Moderate	Minor irreversible health effects to individuals and/or reversible medium term adverse health effects to larger (but surrounding) community (requiring hospitalisation) Measurable long term damage to local plant and animal communities, but no obvious spread beyond defined boundaries, medium term individual ecosystem damage, no species damage Medium term (one to five years) regional adverse economic effects with some national implications, medium term job losses Some social disruption (e.g. people delayed)
Major	Significant irreversible adverse health effects affecting individuals and requiring hospitalisation and/or reversible adverse health effects reaching beyond the immediate community Long term/irreversible damage to localised ecosystem but no species loss Measurable adverse effect on GDP, some long term (more than five years) job losses Social disruption to surrounding community, including some evacuations
Massive	Significant irreversible adverse health effects reaching beyond the immediate community and/or deaths Extensive irreversible ecosystem damage, including species loss Significant on-going adverse effect on GDP, long term job losses on a national basis Major social disruption with entire surrounding area evacuated and impacts on wider community

Table 2 Magnitude of beneficial effect (benefits)

Descriptor	Examples of descriptions -BENEFICIAL
Minimal	Mild short term positive health effects to individuals in highly localised area Highly localised and contained environmental impact, affecting a few (less than ten) individuals members of communities of flora or fauna, no discernible ecosystem impact Local/regional short-term beneficial economic effects on small organisations (businesses, individuals), temporary job creation No social effect
Minor	Mild short term beneficial health effects to identified and isolated groups Localised and contained beneficial environmental impact, no discernible ecosystem impact Regional beneficial economic effects on small organisations (businesses, individuals) lasting less than six months, temporary job creation Minor localised community benefit
Moderate	Minor health benefits to individuals and/or medium term health impacts on larger (but surrounding) community and health status groups Measurable benefit to localised plant and animal communities expected to pertain to medium term. Medium term (one to five years) regional beneficial economic effects with some national implications, medium term job creation Local community and some individuals beyond immediate community receive social benefit.
Major	Significant beneficial health effects to localised community and specific groups in wider community Long term benefit to localised ecosystem(s) Measurable beneficial effect on GDP, some long term (more than five years) job creation Substantial social benefit to surrounding community, and individuals in wider community.
Massive	Significant long term beneficial health effects to the wider community Long term, wide spread benefits to species and/or ecosystems Significant on-going effect beneficial on GDP, long term job creation on a national basis Major social benefit affecting wider community

The likelihood applies to the composite likelihood of the end effect, and not either to the initiating event, or any one of the intermediary events. It includes:

- the concept of an initiating event (triggering the hazard), and
- the exposure pathway that links the source (hazard) and the area of impact (public health, environment, economy, or community).

Thus, the likelihood is not the likelihood of an organism escaping, or the frequency of accidents for trucks containing hazardous substances, but the likelihood of the specified adverse effect[13] resulting from that initiating event. It will be a combination of the likelihood of the initiating event and several intermediary likelihoods[14]. The best way to determine the likelihood is to specify and analyse the complete pathway from source to impact.

Likelihood may be expressed as a frequency or a probability. While frequency is often expressed as a number of events within a given time period, it may also be expressed as the number of events per head of (exposed) population. As a probability, the likelihood is dimensionless and refers to the number of events of interest divided by the total number of events (range 0-1).

[13] The specified effect refers to scenarios established in order to establish the representative risk, and may be as specific as x people suffering adverse health effects, or y% of a bird population being adversely affected. The risks included in the analysis may be those related to a single scenario, or may be defined as a combination of several scenarios.

[14] Qualitative event tree analysis may be a useful way of ensuring that all aspects are included.

Table 3 Likelihood

Descriptor	Description
Highly improbable	Almost certainly not occurring but cannot be totally ruled out
Very unlikely	Considered only to occur in very unusual circumstances
Unlikely (occasional)	Could occur, but is not expected to occur under normal operating conditions.
Likely	A good chance that it may occur under normal operating conditions.
Highly likely	Almost certain, or expected to occur if all conditions met

Using the magnitude and likelihood tables a matrix representing a level of risk/benefit can be constructed.

In the example shown in Table 4, four levels of risk/benefit are allocated: A (negligible), B (low), C (medium), and D (high). These terms have been used to avoid confusion with the descriptions used for likelihood and magnitude, and to emphasise that the matrix is a tool to help decide which risks/benefits require further analysis to determine their significance in the decision making process.

For negative effects, the levels are used to show how risks can be reduced by the application of additional controls. Where the table is used for positive effects it may also be possible for controls to be applied to ensure that a particular level of benefit is achieved, but this is not a common approach. The purpose of developing the tables for both risk and benefit is so that the risks and benefits can be compared.

Table 4 Level of risk

	Magnitude of effect				
Likelihood	**Minimal**	**Minor**	**Moderate**	**Major**	**Massive**
Highly improbable	A	A	A	B	B
Very unlikely	A	A	B	B	C
Unlikely	A	B	B	C	C
Likely	B	B	C	C	D
Highly likely	B	C	C	D	D

APPENDIX 7: GOVERNMENT DEPARTMENTS, CROWN ENTITIES AND INTERESTED PARTIES NOTIFIED

Aakland Chemicals (1997) Limited
AgBio Research Limited
AgResearch Limited
Agronica New Zealand Limited
Ancare Scientific Limited
ARPPA
BASF New Zealand Limited
Bayer New Zealand Limited
BOC Limited
Bomac Laboratories Limited
Caltex New Zealand Limited
Central Hawkes Bay District Council
Chancery Green
Chemagro New Zealand Limited
Chemsafety Limited
Crown Public Health
CSD Consultancy Ltd
Donaghys Industries Limited
Dow AgroSciences (New Zealand) Limited.
DuPont (New Zealand) Limited
Environment Southland
Environment Waikato
Far North District Council
Federated Farmers of New Zealand (Incorporated)
Fish and Game Council of New Zealand
Fish and Game Eastern Region
Franklin District Council
GE Free (Wairarapa)
General Cable New Zealand Limited
Greater Wellington - The Regional Council
Green Party of Aotearoa New Zealand
Horticulture and Food Research Institute (HortResearch)
HQ Joint Forces New Zealand
Human Rights Commission
Hunt Agencies Limited
IMCD New Zealand Limited
Intervet Limited
Kaipara District Council
Kawerau District Council
Landcorp Farming Limited
Lowndes Associates
MackeNew Zealandie District Council
MAF Biosecurity New Zealand (MAFBNew Zealand)
Matamata-Piako District Council
Merial New Zealand Limited

Ministry of Research Science and Technology (MoRST)
Muaupoko Co-operative Society
Napier Health Centre - Public Health Unit
National Aquarium of New Zealand
National Institute of Water and Atmospheric Research Limited (NIWA)
New Plymouth District Council
New Zealand Chemical Industry Council Inc
New Zealand Customs Service
New Zealand Meatworkers Union
New Zealand Press Association
New Zealand Society of Gunsmiths Inc
New Zealand Veterinary Association Inc
New Zeland Bee Industry Group - Federated Farmers
Ngati Kahungunu Iwi Incorporated
Northern Chemical Workers Union
Northland Health
Northland Regional Council
Nufarm New Zealand Limited
Nursery and Garden Industry Association of New Zealand Inc
Otago District Health Board
Pacific Growers Supplies Limited
Pesticide Action Network Aotearoa New Zealand
Pfizer New Zealand Limited
PharmVet Solutions
Physicians and Scientists for Global Responsibility (PSGR)
Rangitikei District Council
Reckitt Benckiser
Royal Forest and Bird Protection Society of New Zealand Inc.
Rural and Associated Contractors Federation of New Zealand
South Taranaki District Council
Spraywatchers Group
Sustainability Council of New Zealand
Syngenta Crop Protection Limited
Tairawhiti District Health
Taranaki Regional Council
Tasman District Council
Te Pataka Matauranga Charitable Trust
Technical Strategy Group Limited
Television New Zealand
Thames Coromandel District Council
The Green Party of Aotearoa New Zealand Inc
The National Beekeepers Association of New Zealand
TMP Consultancy
University of Auckland
Veg-Gro Supplies Limited
ViaLactia Biosciences (New Zealand) Limited
Virbac Laboratories New Zealand Limited
Yates Australia
Zelam Limited
10 Private Individuals

APPENDIX 8: CONFIDENTIAL MATERIAL

APPENDIX 9: CONFIDENTIAL MATERIAL