CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-911

ENVIRONMENTAL ASSESSMENT

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 11, 2006

From: Bai Nguyen, M.S. Chemist, OPS, CDER, FDA, HFD-354

To: Administrative Files: NDA 21-911

Subject: Finding of No Significant Impact (FONSI) for Inovelon Oral Tablet 100, 200 and 400 mg

The following FONSI was completed after reviewing the corresponding environmental assessment by contract reviewer, Dr. Ruth Ganunis (reference number: 1007548). As a chemist reviewer from the Office of Pharmaceutical Science/IO and a supervisor for this project, I am responsible for technical content as well as for entering this FONSI into the Division File System (DFS). If you have questions regarding this review, please feel free to contact me directly.

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drugs Evaluation and Research

Memorandum

Date: September 06, 2006

From: Bai Nguyen, M.S. Chemist, OPS, CDER, FDA, HFD-354

To: Administrative Files: NDA 21-911

Subject: Review of Environmental Assessment Inovelon Oral Tablets 100, 200 and 400 mg

The following review of Environmental Assessment was completed by a contract reviewer, Dr. Ruth Ganunis (reference number: 1007548) according to FDA current policies and guidance. As a chemist reviewer from Office of Pharmaceutical Science/IO and a supervisor for this project, I am responsible for technical content as well as entering of the review into Division File System. If you have any questions regarding this review, please feel free to contact me directly.

REVIEW

OF

ENVIRONMENTAL ASSESSMENT

FOR

Inovelon Oral Tablets
100, 200 & 400 mg

NDA 21-911

Antiepileptic

Food and Drug Administration
Center for Drug Evaluation and Research

Office of New Drug Quality Assessment

September 3, 2006

Environmental Assessment Review #1, NDA 21-911
Inovelon Tablets

Executive Summary

A FONSI is recommended.

NDA 21-911 requests approval of Inovelon Tablets, containing rufinamide, for the treatment of partial-onset seizures and Lennox-Gastaut syndrome.

The firm estimates that the highest amount of rufinamide manufactured for all indications for the US market in any of the next five years is expected to be 74,077 kg/year. This peak production corresponds to an EIC of 1.67 ppb in the aquatic environment. Rufinamide is extensively (approximately 95%) metabolized in humans. The EIC adjusted for deactivation by metabolism prior to entering the environment is 0.08 ppb. Since the metabolically adjusted value is significantly below the threshold level of 1 ppb and no potential adverse environmental effects were identified in the EA, the firm would have qualified for a categorical exclusion had they requested it.

The firm provides environmental fate and effects data which demonstrate that rufanimide is not expected to be toxic to aquatic organisms at expected concentrations.

No inhibition of respiration of activated sludge was observed at concentrations up to 100 mg/L. The 48-hour EC_{50} for the most sensitive organism *daphnia magna* is > 28.7 mg/L. This EC_{50} value divided by the MEEC (using an EIC of 1.67 ppb) is significantly greater than 1000, the tier 1 assessment factor. In addition, there are no observed effects at the MEEC.

A FONSI is recommended for NDA 21-992.

Environmental Assessment Review #1, NDA 21-911
Inovelon Tablets

It was noted during a preliminary review (August 14, 2006) of the June 13, 2005 EA that each page was marked confidential. The EA summary document and nonconfidential appendices are made available to the public (21 CFR 25.50(a) and (b)) and therefore should not contain confidential information, and should not be marked confidential. All confidential information should be located in a confidential appendix. The firm was contacted and this information was relayed to Robert J Clark of Eisai Medical Research Inc. on 8/14/06. In their August 24, 2006 resubmission of the June 13, 2005 document, the firm agreed that the summary document could be released to the public as is, and removed confidential from the header. The entire June 13, 2005 EA was resubmitted on August 24, 2006, and is the subject of the following review.

1. **DATE:** EA prepared: June 13, 2005

2. **APPLICANT:** Eisai Medical Research Inc.

3. **ADDRESS:** 55 Challenger Road
Ridgefield Park, New Jersey 07660

4. **PROPOSED ACTION:**

a. **Requested Approval:**

NDA 21-911 requests approval of Inovelon Tablets for the treatment of partial-onset seizures and Lennox-Gastaut syndrome. Inovelon Tablets, containing 100 mg, 200 mg or 400 mg of rufinamide, will be packaged in aluminium/aluminium blister strips. An EA has been submitted pursuant to 21CFR part 25.

Adequate

b. **Need for Action:**

Inovelon is intended for adjunctive treatment of partial-onset seizures in adults and adolescents of 15 years of age and older, and for adjunctive therapy in seizures associated with Lennox-Gastaut syndrome in children of 4 years and older and adults.

Adequate

c. **Expected Locations of Use (Drug Product):**

The drug will be used in hospitals, clinics and private homes of patients.

Adequate

d. Disposal Sites:

Unused product and packaging will be disposed of according to hospital, pharmacy and clinic procedures. Waste product and packaging arising from private households will be disposed of according to the community's solid waste management policy, typically landfill and incineration.

Adequate

5. IDENTIFICATION OF CHEMICALS

Established name (USAN): Rufinamide

Brand/Proprietary Name/Tradename: Inovelon®

Chemical Name: 1-[(2,6-Difluorophenyl)methyl]-1*H*-1,2,3-triazole-4-carboxamide

IUPAC Name: 1-[(2,6-Difluorobenzyl)-1*H*-1,2,3-triazole-4-carboxamide

CAS Number: 106308-44-5

Molecular Formula: $C_{10}H_8F_2N_4O$

Molecular Weight: 238.2

Structural Formula: Provided on page 4

Physical Description: A fine white powder (page 6)

Adequate

6. ENVIRONMENTAL ISSUE:

a. Identification of Substances of Interest

Rufinamide is extensively (approximately 95%) metabolized in humans. The primary metabolite is the acid derivative of the parent formed by hydrolysis of the carboxylamide group. In addition, the firm has identified three other minor metabolites, one known and two putative. These metabolites/degradants showed no pharmacodynamic activity. Therefore, the drug itself, rufinamide, has been studied as the worse-case representative of all substances entering the environment.

There are no expected environmental risks associated with the excipients and packaging

materials.

Adequate

b. Physical and chemical characterization:

The solubility of rufinamide ranges from insoluble to slightly soluble in the range of solvents tested (see page results page 8). In water, the solubility of rufinamide is 31 mg/L, which is less than 0.01% at 25°C.

Since rufinamide is mostly insoluble in water, it is unlikely to volatilize and partition to the atmospheric phase from water. The risk to the atmospheric compartment is negligible.

A log of the n-octanol/water partition coefficient (log K_{ow}) value of 3 or greater indicates that the substance may absorb to the organic fraction of soil, sediment or biosolid (sewage sludge) and bioaccumulate. The log K_{ow} for rufinamide is 0.65, and is significantly below the threshold for concern.

Rufinamide is a neutral compound, and does not act as an acid or base in aqueous solution.

The firm does not consider further determination of environmental persistence data, such as soil and water half-lives, necessary because of the extensive human metabolism, the low predicted environmental concentration, the low log K_{ow}, and the low environmental toxicity (see related discussions below).

A summary of the physical-chemical characteristics of rufinamide is as follows:

Physical-chemical characteristics	
Water solubility	31 mg/L at 25°C in water
Solubility in other solvents	Very slightly to slightly soluble in a range of solvents tested (see page 8, table 5)
Dissociation Constant	Does not dissociate in the pH range 1-10
Log K_{ow}	0.65, indicating a low potential for bioaccumulation
UV-Vis Adsorption spectrum	3 maxima: 208 nm, 262 nm, and 267 nm
Melting Temperature	233-238°C

c. Environmental depletion mechanisms:

Metabolism of rufinamide in humans is extensive. Less than 2% of the dose was recovered unchanged in urine, and less than 2% was recovered unchanged in feces. The primary metabolite is the acid derivative of the parent formed by hydrolysis of the carboxylamide group. *In-vivo* pharmacodynamic studies on the main metabolite as well as another known metabolite and two putative metabolites showed no pharmacodynamic

activity. The studies conclude that since 95% of rufinamide is metabolically deactivated, only 5% of rufinamide will be environmentally available.

The firm measured biodegradation using a modified Sturm test. OECD Guidelines and Principles of Good Laboratory Practice were followed. The results indicated that rufinamide is not readily biodegraded, although some biodegradation is seen (less than 10% biodegraded by activated sludge). Since rufinamide has been shown to be almost completely metabolized in the human, and the predicted levels of rufinamide in the environment are extremely low, the environmental risk is considered insignificant.

Aerobic and anaerobic transformation in aquatic-sediment systems was not investigated due to the extensive metabolism, low predicted environmental levels, and low toxicity to aquatic organisms of rufinamide.

In a photostability test, rufinamide was found to not be sensitive to light.

Rufinamide is hydrolyzed when exposed at concentrations of 0.5% in solution in acidic (0.1N hydrochloric acid) or basic (0.1N sodium hydroxide) media at 100°C for three days.

A summary of the depletion mechanisms is as follows:

Depletion mechanisms	
Hydrolysis	Hydrolysis/degradation possible
Biodegradation	Not readily biodegradable (approx 10% biodegraded in modified Sturm test)
Photolysis	Tests show lack of photosensitivity
Metabolism	Extensively metabolized in humans (approximately 95%) and other mammals

d. Environmental partitioning

Rufinamide will enter into the environment through publicly owned sewage treatment facilities. Since rufinamide is not soluble, it is unlikely to move to the atmospheric system, into the sediment system, or to pass as a dissolved chemical through the gills of fish. It may concentrate with sediment at the bottom of the water body or as solids suspended in the water. The exposure method for aquatic life forms such as fish or daphnia would be from feeding.

e. Environmental Concentrations

The target population is 138,100 patients (125,800 for adults with partial-onset seizure and 12,300 for patients with Lennox-Gastaut Syndrome). Considering treatment of the entire target population with an average dose, the firm estimates that the highest quantity of active

moiety expected to be produced in any of the next five years to be 74,077 kg/year. This peak production corresponds to an EIC of 1.67 ppb in the aquatic environment (p 13). In this calculation, the firm assumed no metabolism. The firm provided data to the EA (discussed above) that suggests that 95% of a dose is inactivated by human metabolism. The EIC adjusted for metabolism prior to entering the environment, as permitted in the *Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications*, is 0.08 ppb. Since this value is significantly below the threshold level of 1 ppb and no other data submitted to this EA that would have suggested another environmental concern, the firm would have qualified for a categorical exclusion had they requested it.

Some substance may enter the terrestrial environment when biosolids from waste-water treatment facilities are spread to land. Based on the high metabolism by humans, low predicted environmental concentrations, low log K_{ow}, and low toxicity to aquatic organisms, the risk of negative effects from this route is considered to be negligible.

f. Environmental Effects:

The firm assessed the environmental effects of rufinamide by completing a microbial respiration inhibition test, a freshwater algal growth inhibition test, and an acute toxicity test. All tests were performed in accordance with OECD Guidelines, and were provided in the confidential appendices.

Rufinamide did not inhibit growth of the freshwater algae *Selenastrum capricornutum* at any of the concentrations tested. It was concluded that the NOEC and the EC_{50} for both cell growth inhibition and for growth rate reduction exceeded the 33 mg/l maximum solubility of rufinamide in water.

An acute toxicity test was performed on *daphnia magna*. The NOEC and EC_{50} for immobilization of daphnia magna were greater than 100 mg/L nominal (28.7 mg/L analyzed at 48 hours, in agreement with the maximum water solubility of rufinamide).

No significant inhibition in the respiration rate of the activated sludge was observed at 100 mg/L rufinamide.

A summary of the Environmental Effects data is as follows:

Environmental Effects	
Algal Growth Inhibition Test (*Selenastrum capricornutum*)	No growth inhibition detected NOEC > 33 mg/L EC_{50}> 33 mg/L
Acute Toxicity (*Daphnia magna*)	NOEC > 28.7 mg/L at 48 hr EC_{50}> 28.7 mg/L at 48 hr
Activated sludge respiration inhibition test using waste-water bacteria	NOEC > 100 mg/L

The tier 1 assessment factor, namely EC_{50} divided by the MEEC for the most sensitive organism is 1000. In this case, the EC_{50} for *Daphnia magna* (28,700 μg/L) divided by the MEEC (=EIC=1.67 μg/L) is greater than 1000 (at 17185), indicating that environmental effects are not expected. If deactivation by metabolism is considered and an EIC of 0.08 μg/L is used, as is permitted by the *Guidance for Industry: Environmental Assessment of Human Drugs and Biologics Applications*, this value would be even greater (3.6×10^5). In addition, there are no observed effects at the MEEC. Therefore, rufinamide is not expected to negatively impact sludge microflora in wastewater treatment plants at expected concentrations.

A FONSI is recommended for NDA 21-911.

Adequate

VII MITIGATION MEASURES

Information not required because no potential adverse environmental effects have been identified.

Adequate

VIII ALTERNATIVES

Information not required because no potential adverse environmental effects have been identified.

Adequate

IX PREPARER

The preparers and their CVs are provided.

Adequate

X REFERENCES

None provided.

Adequate

XI APPENDICIES

The firm provided the following confidential appendices:

Confidential Appendix A: Measurement of K_{ow}
Confidential Appendix B: Measurement of ready biodegradation using modified Sturm test
Confidential Appendix C: Microbial respiration inhibition test
Confidential Appendix D: Freshwater algal growth inhibition test
Confidential Appendix E: *Daphnia magna* toxicity test

Adequate

Review by: Ruth Ganunis, Ph.D. on September 3, 2006
Chemist, Center for Drug Evaluation and Research

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1.0 GENERAL INFORMATION

Date Report Prepared 13th June 2005

Name of Applicant Eisai Medical Research Inc.

Address 55 Challenger Road
Ridgefield Park
New Jersey 07660

Description of Proposed Action

Requested approval: Eisai Medical Research Inc. has filed an NDA pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for INOVELON® Tablets containing 100 mg, 200 mg or 400 mg of rufinamide, packaged in aluminium/aluminium blister strips. An EA has been submitted pursuant to 21 CFR part 25.

Need for action: INOVELON® is intended for adjunctive treatment of partial-onset seizures in adults and adolescents of 15 years of age and older, and for adjunctive therapy in seizures associated with Lennox-Gastaut syndrome in children of 4 years and older and adults.

Locations of use: Hospitals, clinics and in the private homes of patients.

Disposal sites: Unused product and packaging will be disposed of according to hospital, pharmacy and clinic procedures. Waste product and packaging arising from private households will be disposed of according to the community's solid waste management policy, typically landfill and incineration.

2.0 INTRODUCTION

INOVELON® Tablets are film-coated formulations of rufinamide (INN) for oral use. Dosage strengths containing 100 mg, 200 mg or 400 mg of rufinamide are available.

INOVELON® is intended for adjunctive treatment of partial-onset seizures in adults and adolescents of 15 years of age and older, with the daily dose ranging from 800 to 3200 mg/day.

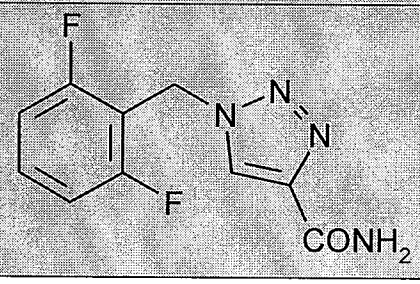
Daily doses range from 10 mg/kg/day (expressed on a kg bodyweight basis) for children and 800 mg/day for adults to 3200 mg/day for adjunctive therapy in seizures associated with Lennox-Gastaut syndrome in children of 4 years and older and adults.

An environmental assessment has been conducted to further demonstrate the negligible environmental risk from the use of INOVELON® for the treatment of two medically important conditions, partial-onset seizures and Lennox-Gastaut syndrome.

As discussed in this Environmental Assessment, the environmental risk from rufinamide is very low and the Expected Introduced Concentration for the aquatic compartment (EIC-Aquatic) is only slightly above the FDA threshold level of 1 ppb at 1.67 ppb (μg/L), as detailed in section 5.2.2 (II). Further refinement of the EIC-Aquatic to derive the Expected Environmental Concentration for the aquatic compartment (EEC-Aquatic) results in a very low level of 0.008 μg/L (see section 5.4.2).

3.0 IDENTIFICATION OF RUFINAMIDE

Table 1: Data for identifying the substance

(a) Nomenclature • Established name • Brand name • Chemical Abstracts Index Name • Systematic Chemical Name (IUPAC)	 Rufinamide INOVELON® 1-[(2,6-Difluorophenyl)methyl]-1*H*-1,2,3-triazole-4-carboxamide 1-(2,6-Difluorobenzyl)-1*H*-1,2,3-triazole-4-carboxamide
(b) Chemical Abstracts Service Registration Number (CAS)	106308-44-5
(c) Molecular Formula	$C_{10}H_8F_2N_4O$
(d) Molecular Weight	238.2
(e) Structural Formula (graphic)	

4.0 DATA SUMMARY TABLE FOR RUFINAMIDE

Table 2: Summary of fate and ecotoxicology data for rufinamide

PHYSICAL-CHEMICAL CHARACTERISTICS	
Water Solubility	31 mg/l at 25°C in water
Solubility in other solvents	Very slightly to slightly soluble in a range of other solvents as described in Table 5 section 5.1.2
Dissociation Constant(s)	Does not dissociate in the pH range 1-10
Log Octanol/Water Partition Coefficient (log K_{ow})	0.65 indicating a low potential for bioaccumulation
UV-Visible Adsorption spectrum	3 maxima: 208 nm, 262 nm & 267 nm
Melting Temperature	233-238°C
DEPLETION MECHANISMS	
Hydrolysis	Hydrolysis/degradation possible
Biodegradation	Not readily biodegradable (approx. 10% biodegraded in modified Sturm test)
Photolysis	Tests show a lack of photosensitivity
Metabolism	Extensively metabolised in humans (approx. 95%) and in other mammals
ENVIRONMENTAL EFFECTS	
Algal Growth Inhibition Test (*Selenastrum capricornutum*)	No growth inhibition detected. NOEC > 33 mg/l
Acute toxicity *Daphnia magna*	NOEC > 28.7 mg/l
Activated sludge respiration inhibition test using waste-water bacteria	NOEC > 100 mg/l

5.0 ENVIRONMENTAL ISSUES

5.1 Environmental Fate

5.1.1 Identification of substances potentially released

Rufinamide, the parent substance, is a fine white powder taking the chemical name of 1-(2,6-Difluorobenzyl)-1*H*-1,2,3-triazole-4-carboxamide and has the molecular formula of $C_{10}H_8F_2N_4O$. It is formulated for use as tablets for oral ingestion.

The metabolism of rufinamide in humans is extensive as described in section 5.1.3 (I).

Metabolites/degradants that may be found in very low amounts in the environment are summarised in Table 3 alongside their identification nomenclature. However, as detailed in section 5.1.3 (I), these substances showed no pharmacodynamic activity suggesting that metabolism, as may be expected, is deactivating. Therefore, the parent material, rufinamide, has been studied as the worse-case representative of all substances entering the environment.

Table 3: Summary of substances potentially active in the environment

Parent material - Rufinamide	
• Brand name	INOVELON® containing rufinamide
• Systematic Chemical Name	1-(2,6-Difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide
• Chemical Abstracts Service Registration Number (CAS)	106308-44-5
Primary human metabolite	
• Identification	GCP 47292
• Description	Acid derivative of parent formed by hydrolysis of the carboxylamide group
Other metabolites	
• GCP 47291	Known
• GCP 47293	Putative
• GCP 47294	Putative

The excipients and packaging materials (given in Table 4 below) are all commonly used in medicinal products particularly those used for oral dosing. There are no expected environmental risks associated with these substances.

Table 4: Excipients and packaging components used in Rufinamide Tablets.

Component	Function
Excipients in Rufinamide tablet Core	
Lactose monohydrate	Filler
Cellulose microcrystalline	Filler
Maize starch	Filler, disintegrant
Croscarmellose sodium	Disintegrant
Hypromellose	Binder
Magnesium stearate	Lubricant
Sodium lauril sulphate	Surfactant
Silica colloidal, anhydrous	Anti-adherent, glidant
Water (removed during processing)	Granulating liquid
Film-coating on tablets	
Opadry *(pre-mixed coating agent consisting of hypromellose, macrogols (8000), titanium dioxide & red ferric oxide (E172)*	Coating and colouring agent
Water (removed during processing)	Aqueous solvent
Container	
Aluminium/aluminium blister strip	Primary packaging

5.1.2 Physical and chemical characterisation

The physico-chemical properties of a chemical are important when assessing the environmental risk as these affect the ability and tendency of that chemical to partition in the environment. They also influence its potential for bioaccumulation and environmental persistence. The physico-chemical data, as described below, are provided in Module 3, with the exception of the n-Octanol/Water partition coefficient (K_{OW}) report, which is provided in Section 8.1, Appendix A.

(I) Solubility

The solubility of rufinamide ranges from slightly soluble to practically insoluble in a range of solvents as detailed in Table 5 below. Rufinamide is considered insoluble at 25°C in aqueous solution having a solubility of only 31 mg/l, which is less than 0.01%. This will influence, to a degree, the mobility of the chemical in various environmental compartments.

Table 5: Solubility of rufinamide in various solvents.

Solvent	mg/l at 25°C	Solubility at 25°C % (g/100 ml solution)	Description
Water	31	< 0.01	Insoluble
0.9% NaCl in water	28	< 0.01	Insoluble
5% Glucose in water	29	< 0.01	Insoluble
0.1N Hydrochloric acid	29	< 0.01	Insoluble
Buffer solution pH 1	29	< 0.01	Insoluble
Buffer solution pH 6.8	28	< 0.01	Insoluble
Buffer solution pH 10	27	< 0.01	Insoluble
Methanol	1219	0.12	Slightly soluble
Ethanol abs.	440	0.04	Very slightly soluble
Acetonitrile	878	0.08	Very slightly soluble
Tetrahydrofurane	1378	0.13	Slightly soluble
	mg/l at 37°C		
Water	69	< 0.01	Insoluble
Simulated gastric fluid	66	< 0.01	Insoluble
Simulated intestinal fluid	38	< 0.01	Insoluble

Description term	Approx. Volume of solvent in wt per litre of solution	In % (g/100ml) solution approx.
Very soluble	>1000 g/l	>100%
Freely soluble	1000 g/l - 100 g/l	10% - 100%
Soluble	100 g/l – 33 g/l	3.3% - 10%
Sparingly soluble	33 g/l – 10 g/l	1% - 3.3%
Slightly soluble	10 g/l – 1 g/l	0.1% - 1%
Very slightly soluble	1 g/l - 100 mg/l	0.01% - 0.1%
Insoluble	<100 mg/l	<0.01%

(II) Volatility

The saturation vapour pressure (P_{vp}) is a measure of the volatility of a chemical in its pure state. It is an important determinant of the rate of vaporisation and for estimating various other intermedia transfer factors (e.g. Henry's law constant (H)).

Both vapour pressure and Henry's Law constant are used to inform on the tendency for the substance to volatilise from aqueous solution to the atmosphere. Rufinamide is insoluble in water and so it is unlikely to volatilise and partition to the atmospheric phase from water. Therefore, the risk to the atmospheric compartment is negligible.

(III) Bioaccumulation Potential

The n-Octanol/Water partition coefficient (K_{OW}) is an indicator of a non-ionised substance's ability to absorb to the organic fraction of soil, sediment or a biosolid (e.g. sewage sludge). It is also used as an indicator of a substance's lipophilicity.

K_{OW} was determined according to the method and test procedure reported in section 8.1, Appendix A. The mean value (from two determinations) for K_{OW} of rufinamide was 4.45. Log K_{OW} was derived from this figure and was calculated to be 0.65 for rufinamide.

A high value for this partition coefficient (i.e. 3 or greater) is considered an indicator that the substance may bioaccumulate unless there are other influencing factors. The log K_{OW} rufinamide value of 0.65 is significantly below this threshold of concern. Additionally, since rufinamide is markedly metabolised in humans, its bioconcentration potential is insignificant. Further study of the sorption/desorption properties (K_{OC}) of rufinamide have therefore not been considered necessary.

(IV) Acid Dissociation

Structurally, rufinamide is a neutral compound and does not act as a base or acid in aqueous solution. Solubility results indicate that rufinamide does not dissociate in the pH range 1-10.

(V) Environmental Persistence

Environmental persistence is an important criterion for assessing the potential risks of long-term exposure to a chemical. However, it is not always an accurate indicator of exposure potential. Chemicals may have extremely long half-lives, but may be sequestered in environmental compartments (like sediments in water) where there is little likelihood of human or other target organism exposure.

In this instance because of the low predicted environmental concentration, the 0.65 log K_{OW}, the extensive human metabolism and low environmental toxicity (as discussed in section 5.3), further determination of environmental persistence data in the form of soil and water half-lives has not been considered necessary.

5.1.3 Environmental depletion mechanisms

(I) Metabolic Transformation

Metabolic transformation of rufinamide in humans has been shown to be extensive (Protocol No. HPH 9213, BPK (F) Project X584; Module 5). Less than 2% of the dose was recovered unchanged in the urine from healthy male volunteers after a single oral dose of 600 mg. Similarly, only 2% of the rufinamide dose was found in faeces. The main metabolite in urine and faeces was CGP 47292, which is an acid derivative of rufinamide formed by the hydrolysis of the carboxylamide group. A number of other metabolites were excreted in urine and faeces. It can be concluded that approximately 95% of rufinamide administered to patients is metabolised, such that only approximately 5% as rufinamide will be environmentally available. This 5% figure has been utilised in the calculation of the Expected Environmental Concentration for the aquatic compartment (EEC-Aquatic) as detailed in section 5.4.2.

Primary pharmacodynamic data (Study BN-3-89; Module 4) using an *in vivo* electrically-induced seizure model have been generated using two known metabolites (CGP 47292, the primary human metabolite, and CGP 47291) and two putative metabolites of rufinamide (CGP 47293, CGP 47294). All of these compounds showed no pharmacodynamic activity and no limiting side effects at oral doses of 60 mg/kg (rat) and 300 mg/kg (mouse). Rufinamide showed activity against seizures at lower doses in both species. It can therefore be concluded that rufinamide is metabolically deactivated, such that the potential for pharmaco-toxicological activity is further reduced.

Rufinamide is significantly metabolised in other mammalian species including mouse, rat, dog, Cynomolgus monkey and baboon (see Module 2, section 2.6.4) and has shown some biodegradation when incubated with aerobic bacteria (see section 5.1.3 (II) below).

(II) Biodegradation

A ready biodegradability modified Sturm test was performed with rufinamide in accordance with OECD Guideline 310 B and OECD Principles of Good Laboratory Practice (section 8.1, Appendix B). Quality assurance inspections of the test on-site and the protocol were performed and the study report was audited. The study was performed using rufinamide batch no. 847197 (99.7 % pure).

This test measures biodegradability (evolution of carbon dioxide) over 28 days (last reading on day 29), during which time the test substance is incubated in an aerobic aqueous medium with microbial activity introduced by inoculation of activated sludge. The theoretical CO_2 production of rufinamide was calculated to be 1.85 mg CO_2/mg. The relative degradation values for duplicate test vessels showed that rufinamide was not significantly (>10%) biodegraded, with values of 8.6% and 7.2% observed at day 29. The positive control test using sodium acetate gave the appropriate result, with 88% biodegradation observed by day 29. In the toxicity control, rufinamide was found not to be inhibitory upon production of CO_2 from sodium acetate.

It can be concluded that rufinamide was not readily biodegraded under the conditions of the modified Sturm test, although some biodegradation was seen. Since rufinamide has been shown to be almost completely metabolised in the human (see section 5.1.3 (I) above), and the predicted levels of rufinamide in the environment are extremely low (see sections 5.2.2 and 5.4.2), the environmental risk is considered insignificant.

(III) Aerobic and Anaerobic transformation in aquatic-sediment systems

Aquatic sediment system transformation data are not available for rufinamide. This is considered to be acceptable in view of the following factors:

- Extremely low predicted environmental levels of rufinamide
- Extensive metabolism of rufinamide in mammals, and some biodegradation by waste-water bacteria (as detailed above in section 5.1.3 (II) and in Appendix B).
- Extremely low toxicity to waste-water bacteria, algae and *Daphnia* from the various studies performed, with expected biodegradation in the aquatic system

(IV) Photolysis

In a photostability test, approx. 1 g of rufinamide was exposed to light (1200 kLuxh; Xenon lamp) as a 3 mm layer in a glass dish. Rufinamide was not sensitive to light under the conditions of the test. The lack of photosensitivity is not considered to be a concern from an environmental perspective, given that rufinamide is extensively metabolised in humans, and is subject to metabolism and degradation in the environment at the extremely low levels at which it will be present.

(VI) Hydrolysis

Rufinamide can undergo hydrolysis and/or degradation when exposed at concentrations of 0.5% in solution in acidic (0.1N hydrochloric acid (HCl)) or basic (0.1N sodium hydroxide) media at 100°C for three days. In chromatograms, an increased peak eluting with the solvent was observed, indicating degradation.

5.2 Environmental Concentrations

5.2.1 Environmental partitioning

Considering the use of rufinamide as an orally administered drug, it can be assumed that it would be introduced into the aquatic environment via publicly owned sewage treatment facilities resulting from the discharge of patients' urine and faeces. As discussed in detail below, no other environmental pathway appears to be viable. However, the potential for its release in the terrestrial environment via the spreading of biosolids is discussed in section 5.2.2 (III).

(I) Aquatic Partitioning

Once in the aquatic environment, the chemical would be expected to partition between distinct parts of that environment e.g. water, sediment, atmosphere, biota etc. Chemicals do not necessarily remain static in their initial entry phase but may physically move from one phase to another and may, theoretically, pass from the aquatic system to the atmosphere and/or terrestrial systems. The extent to which this happens will depend upon the physico-chemical properties of the substance (i.e. rufinamide) and the environmental conditions.

- **Water-aquatic biota system:** The usual mechanism for this is for the dissolved chemical to pass through the gills of fish. Rufinamide is considered to be insoluble in water. Consequently this partitioning pathway is expected to be insignificant. In view of this, the predicted low environmental concentrations and the lack of toxicity to algae and *Daphnia*, toxicity tests for fish have therefore not been conducted.

- **Water-atmosphere system:** Due to the insolubility of rufinamide, volatilisation from the water phase to air would not be expected to occur. Consequently this partitioning pathway is expected to be insignificant.

- **Water-sediment system:** As rufinamide is insoluble in water the quantity moving between the water and sediment phases (either that settled on the bottom of the water body or as suspended solids) would be expected to be insignificant.

- **Sediment-biota system:** This is likely to be the main pathway by which aquatic biota may become exposed to rufinamide. As rufinamide is insoluble it is likely to concentrate within the sediment at the bottom of the water body or as solids suspended in the water. The exposure method for aquatic taxa such as fish or *Daphnia* is therefore likely to be via feeding. No information on the decay rate of rufinamide in water is available.

(II) Atmospheric Partitioning

There is unlikely to be a direct release of the drug to the atmosphere. Atmosphere-vegetation partitioning, atmospheric-biota and atmosphere-soil partitioning could only occur if the chemical could move from the water phase to the atmosphere or from the soil-phase to the atmosphere. As these routes are highly unlikely, the risk of environmental partitioning to the atmosphere is considered negligible.

(III) Terrestrial Partitioning

The chemical is unlikely to reach the terrestrial phase via environmental partitioning due to the absence of a viable pathway from water or atmosphere. However, it could conceivably be deposited directly with biosolids (see section 5.2.2 (III)).

5.2.2 Expected Introduced Concentrations

(I) Atmospheric

Due to the absence of viable environmental partitioning to the atmosphere, the Expected Introduced Concentration for the atmospheric phase (EIC-atmosphere) is considered to be negligible and has not been calculated.

(II) Aquatic

The Expected Introduced Concentration for the aquatic phase (EIC-aquatic) has been determined according to FDA "Guidance for Industry. Environmental Assessment of Human Drug and Biologics Applications", July 1998, CMC 6, Revision 1.

- Target population = 138,100 (125,800 for Adults with partial-onset seizures and 12,300 for patients with Lennox-Gastaut Syndrome).

- Dose levels per day = Child 200 to 3200 mg/day; Adult 400 to 3200 mg/day. Average dose level taken as 1800 mg/day.

- Therapeutic (Tx) Days = 298 out of 365 per year.

- The amount of the active moiety produced for direct use in a year is therefore:

  138,100 x 1800 mg/day x 298 = 74,076,837,000 mg/yr or 74,077 kg/yr*
  * this estimate is the highest quantity of the active moiety expected to be produced in any of the next five years

- EIC-Aquatic (μg/L) = A x B x C x D

  where:
  A = kg/year produced for direct use (as active moiety).
  B = 1/Liters per day entering publicly owned treatment works[1] (POTWs) estimated as 1.214×10^{11} L/day.
  C = 1/365 days = 2.74×10^{-3}.
  D = 10^9 μg/kg (conversion factor)

  EIC-Aquatic_average (μg/L) $= 74{,}077 \times (1/1.214 \times 10^{11}) \times (2.74 \times 10^{-3}) \times 10^9$

  $= 1.67$ ppb (μg/L)

This calculation assumes that:

- all the drug produced for direct use enters the publicly owned treatment works system,
- the drug product usage would occur throughout the USA in proportion to the population and the amount of waste generated
- there is no metabolism

Therefore, the product does not qualify for categorical exclusion and a tiered approach to fate and effects with respect to the aquatic environment has been conducted (see section 5.3).

In practice, this low concentration would be much further reduced due to the extensive human metabolism and further depletion and dilution via various environmental mechanisms (see section 5.4.2).

(III) Terrestrial

Due to the absence of viable environmental partitioning to terrestrial systems directly from the water phase or from the atmosphere the Expected Introduced Concentration for the terrestrial phase (EIC-terrestrial) is considered to be negligible via this pathway.

Some substances may potentially enter the terrestrial environment when biosolids, containing the adsorbed substance, from waste-water treatment facilities are spread to land. Biosolids are generally subject to aerobic or anaerobic digestion at the treatment facility, which may potentially degrade or remove the substance. As detailed in section 5.1.3 (II), rufinamide has been shown to biodegrade to a limited extent (approximately 10%) in a ready biodegradability modified Sturm test.

[1] Data source: 1996 Needs Survey, Report to Congress.

Based on the extremely low predicted environment concentrations and extensive depletion mechanisms, principally human metabolism and also biodegradation by microbial activity, the risk of negative environmental effects from this route is considered to be negligible and so the expected concentration of the drug in the terrestrial phase via the deposition of biosolids has not been calculated.

It is not expected that significant quantities of the drug would be likely to enter the terrestrial environment via disposal routes such as landfill or incineration.

5.3 Environmental Toxicological Assessment

Studies using *Daphnia magna* and freshwater algae (*Selenastrum capricornutum*) have been performed to evaluate the toxicity of rufinamide in the aquatic environment. In addition, a study on the effect of rufinamide on waste-water bacteria was conducted. All studies have been satisfactorily performed according to contemporary standards and in accordance with OECD Guidelines.

5.3.1 Freshwater algal growth inhibition test

A freshwater algal growth inhibition test (section 8.1, Appendix D) was performed in accordance with OECD Guideline 201. Quality assurance inspections of the test on-site and the protocol were performed and the study report was audited. The study was performed using rufinamide batch no. 847197 (99.7 % pure).

A Reference Test for *Selenastrum capricornutum* growth inhibition using potassium dichromate was performed a number of weeks before this test to ensure that the sensitivity of the test method was acceptable. The reference results were in agreement with what was expected on the basis of the historical data.

A range-finding test was first performed at nominal concentrations of 0.1 to 100 mg/L. Microscopic counting of cells at 72 hours was performed due to turbidity of the 100 mg/L solution, affecting spectrophotometric measurements. There was no concentration-related effect of rufinamide on cell density at any concentration.

In the main test, exponentially growing *Selenastrum capricornutum* cultures were exposed to 10, 22, 45 or 100 mg/L over 72 hours under static conditions. The initial cell density was 10^4 cells per ml. Analytical samples were taken at 0 and 72 hours from the 10 and 100 mg/L concentrations. The concentration at the nominal 10 mg/L remained stable (8.4 mg/L at 0 hours and 8.8 mg/L at 72 hours). At the higher nominal concentration of 100 mg/L, the analytical concentrations found were 72-81 mg/L at 0 hours. The concentrations were reduced to 44-55 mg/L by the end of the study. All of these figures remained above the maximum water solubility of 33 mg/L. The results were reported fully in the Analytical Report for the test.

Rufinamide did not inhibit the growth of *Selenastrum capricornutum* at any concentration tested. It was concluded that the No-Observed Effect Concentration (NOEC) and EC50 (0-72 hour) for cell growth inhibition and the NOEC and EC50 (0-72 hour) for growth rate

reduction exceeded the 33 mg/l maximum solubility of rufinamide in water. It has been concluded that rufinamide would not be expected to be acutely toxic to freshwater algae after any kind of spill or discharge.

At the estimated negligible concentrations of rufinamide in the environment resulting from clinical use, the environmental risk to freshwater algae is therefore also negligible (see section 5.4.2).

5.3.2 Acute toxicity study using *Daphnia magna*

An acute toxicity test (section 8.1, Appendix E) with *Daphnia magna* was performed in accordance with OECD Guideline 202. Quality assurance inspections of the test on-site and the protocol were performed and the study report was audited. The study was performed using rufinamide batch no. 847197 (99.7 % pure).

A Reference Test for acute toxicity to *Daphnia magna* using potassium dichromate was performed shortly before this test to ensure that the sensitivity of the test method was acceptable. The reference results were in agreement with what was expected on the basis of the historical data.

A range-finding test was first performed at nominal concentrations of 0.1, 1, 10 and 100 mg/L, using 10 daphnids per concentration. Over 48 hours, there were no immobilised daphnids at any concentration.

The main test was performed as a limit test of 100 mg/L with a blank control, and under static conditions. There were two vessels per test and control group, each containing 10 daphnids per vessel. Analytical samples were taken at the beginning (0 hours) and at the end of the test (48 hours).

At a nominal concentration of 100 mg/L, rufinamide caused no acute toxicity to *Daphnia magna*. The analytical concentrations of rufinamide were 94.8 mg/L at 0 hours and 28.7 mg/L at 48 hours. The latter value is in agreement with the maximum water solubility of rufinamide. Precipitation and test substance deposits were observed in the 100 mg/L test vessels. The analytical results were reported fully in the Analytical Report. In both the control and 100 mg/L groups, no immobilised daphnids were observed at the 24 and 48 hours observation times. The NOEC for immobilisation and EC50 for immobilisation were therefore greater than 100mg/L nominal (28.7 mg/L analysed at 48 hours). It can be concluded that rufinamide would not be expected to be acutely toxic to *Daphnia magna* after any kind of spill or discharge.

At the negligible predicted concentrations of rufinamide in the environment resulting from clinical use, the environmental risk to *Daphnia magna* is therefore also negligible (see section 5.4.2).

5.3.3 Microbial respiration inhibition test

An activated sludge respiration inhibition test was performed in accordance with OECD Guideline 209 (section 8.1, Appendix C). Quality assurance inspections of the test on-site and

the protocol were performed and the study report was audited. The study was performed using rufinamide batch no. 847197 (99.7 % pure).

No significant inhibition in the respiration rate of the activated sludge was observed at 100 mg/L rufinamide, based on two independent assays. Therefore, no further testing was necessary.

The respiration rates of the four control flasks were within 15% of each other. The reference substance, 3,5-dichlorophenol had an EC50 of 9 mg/L. This was within the accepted range of 5-30 mg/L.

It can be concluded that rufinamide showed no toxicity to waste-water bacteria at the very high concentration of 100 mg/L. Given the predicted extremely low levels of rufinamide in the environment resulting from clinical use, the risk to waste-water bacteria is negligible (see section 5.4.2).

5.4 Discussion and evaluation of environmental effects

5.4.1 Effects on and the exposure of rufinamide on terrestrial wildlife

Impact on terrestrial wildlife is considered insignificant due to the low predicted environmental concentrations and extensive human metabolism of rufinamide. There does not appear to be a viable exposure route for terrestrial wildlife.

5.4.2 Effects on and exposure of aquatic organisms

The potential risks associated with the release of a chemical into the environment can be assessed by comparing the Expected Environmental Concentrations (EECs) in various environmental compartments with data describing the toxicity of the chemical to biota that live in that environment.

The Expected Introduced Concentration for the aquatic phase has been estimated as a maximum and as an actual value using the method given in section 5.2.2 (II).

EIC-Aquatic_average (μg/L) = 1.67 μg/l

The Expected Environmental Concentration (EEC) as specified in the FDA Guidance for Industry (July 1998) allows for a dilution factor of 10 to the EIC-Aquatic to estimate the EEC-Aquatic. In addition, since rufinamide is nearly completely metabolised (approximately 95%) in patients, the EEC-Aquatic has been calculated to be:

EEC-Aquatic (μg/L) = 0.008 μg/l

This figure is considerably less (125 times) than the FDA action threshold of 1 ppb (1 μg/L).

Ecotoxicological studies have been performed using the freshwater alga (*Selenastrum capricornutum*), *Daphnia magna* and waste-water bacteria. Table 6 below gives the NOEC values for the tests performed and the calculated ratios of the Predicted No Effect Concentrations (NOEC) : EEC-Aquatic.

Table 6: Hazard and Risk Assessment for Rufinamide using Ecotoxicological (Aquatic and Microbial) Studies

Ecotoxicological Study	NOEC	TER (NOEC/EEC-Aquatic*)
Freshwater algal growth inhibition test using *Selenastrum capricornatum*	NOEC > 33 mg/L (33,000 µg/L)	4.13×10^6
Acute toxicity test using *Daphnia magna*	NOEC > 28.7 mg/L (28,700 µg/L)	3.6×10^6
Activated sludge respiration inhibition test using waste-water bacteria	NOEC > 100 mg/L (100,000 µg/L)	1.25×10^7

* EEC-Aquatic = 0.008 µg/l

Table 6 shows extremely high toxicity:exposure ratios for two aquatic species and for microbial inhibition. All values are significantly above the 1000 assessment factor stipulated in FDA Guidance (July 1998). Even if the maximum value of the EIC-Aquatic is used, the values are much greater than this assessment factor. Taking into account the extremely low levels of rufinamide that will be present in the environment and the ethical perspective, it would not be appropriate to undertake an *in vivo* acute toxicity test using fish. No further testing has been considered necessary.

5.4.3 Other factors affecting the environmental risk

There are no environmental risks associated with the impurities and degradation products of the drug substance, rufinamide. As a specification, these are limited to ≤ 0.5% of the drug product. Therefore, the quantities of these related substances introduced into the environment will be extremely low. The specification for the residual solvent, methanol, in the drug substance is ≤0.1%. This also represents an extremely low environmental burden for this solvent, such that the environmental risk is insignificant. The validation batches of rufinamide drug substance in fact show lower values for methanol (≤ 0.01%) and total related substances (≤ 0.05%).

There are no environmental hazards from the use of the excipients in INOVELON® Tablets as detailed in Table 4. These excipients are commonly used in other tablet formulations. The packaging is also standard for tablet formulations.

As detailed in this document, a step-wise and phased assessment for INOVELON® Tablets has been conducted encompassing rufinamide, metabolites, impurities/degradation products, excipients and packaging.

5.5 Summary and Conclusion

No potential adverse environmental effects have been identified for the proposed action. Metabolism and degradation of rufinamide occurs in humans, other mammals and in waste-water bacteria. Rufinamide can be degraded also by hydrolysis. The log n-Octanol/Water partition coefficient (K_{OW}) for rufinamide is 0.65, suggesting that there is negligible bioaccumulation potential from this substance.

Environmental exposure will be negligible in the atmospheric and terrestrial compartments. The Expected Introduced Concentration for rufinamide in the aquatic compartment (EIC-Aquatic) is only slightly above the FDA threshold level of 1 ppb at 1.67 ppb (μg/L). Further refinement of the EIC-Aquatic to derive the Expected Environmental Concentration for the aquatic compartment (EEC-Aquatic) results in an extremely low level of 0.008 μg/L. By comparing the EEC-Aquatic with the NOEC values from algal growth inhibition, acute toxicity in *Daphnia* and activated sludge respiration inhibition tests, extremely large toxicity:exposure ratios have been calculated. These findings clearly demonstrate the lack of environmental risk to the aquatic compartment.

Based on the product characteristics for INOVELON® Tablets and the information provided in this Environmental Assessment, it can be concluded that the environmental risk from the use, storage and disposal of this product is negligible and that no further testing is warranted.

6.0 MITIGATION MEASURES

No potential adverse effects have been identified and, therefore, no mitigation measures are needed.

7.0 PREPARERS

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QUALIFICATIONS:

1982 - 1986 **BSc. (Hons, 2.1): Applied Biology** University of Wales Institute of Science and Technology, Cardiff, UK

1986 - 1987 **Master of Science: Toxicology** University of Surrey, Guildford, UK

PROFESSIONAL EXPERIENCE:

From August 2004 **ProPhase Development Ltd:** Director

- Specialist toxicology/nonclinical consultancy
- Toxicology/nonclinical expert
- Toxicology/nonclinical evaluations and summaries
- Strategic product development consulting
- Member of biotech steering teams

Aug 2003 – Aug 2004 **Quintiles UK Limited:** Associate Director, Regulatory

- Provision of specialist toxicology/nonclinical, regulatory, and pharmaceutical/biotech development consultancy and services
- Toxicology/nonclinical expert
- *Ad hoc* membership of strategic development teams
- Project management and due diligence services
- Management of regulatory team

Feb 2001 – Aug 2003 **Daiichi Pharmaceuticals UK Ltd:** Senior Regulatory Manager (promoted from Regulatory Manager, Jan 2003)

- Member of management team
- Regulatory advice, project management and strategic planning

- Strategic input into clinical development programmes, early developmental (including first-in-man phase I) programmes, and in-licensing opportunities
- Preparation and review of regulatory documentation, regulatory agency briefing documents, and investigator brochures
- Meetings, scientific advice submissions and other communications with EU regulatory agencies
- Provision of specialist regulatory nonclinical/toxicology expertise to development programmes
- Management of and liaison with CROs and external consultants

Aug 1998 - Jan 2001

Quintiles UK Limited: Senior Regulatory Consultant (promoted from Regulatory Affairs Specialist in August 1999)

- Provision of regulatory advice, project management and strategic planning from early development to regulatory approval
- Provision of specialist regulatory toxicology/nonclinical expertise
- Preparation and review of regulatory documentation and expert reports for submission to EU regulatory agencies
- Responsible expert for pharmaco-toxicology expert reports
- Member of strategic/submission teams for pharmaceutical companies

1998

Pharmakopius International Ltd: Regulatory Affairs Manager

- Toxicology/nonclinical and clinical data evaluation. Toxicology advisor to clients

1996 - 1998

Pfizer Central Research: Regulatory Scientist (Senior Scientist)

- Provision of regulatory advice to other Pfizer scientists for development programmes of candidate animal health products
- Responsible for sections of regulatory dossiers and for submitting regulatory (MAA, MRL, animal trials) dossiers to European regulatory agencies, including the EMEA/CVMP

1988 - 1996

Pesticides Safety Directorate: Regulatory Toxicologist (Senior Scientific Officer, promoted from Higher Scientific Officer in 1990)

- Assessor of pesticide toxicology and pharmacokinetic/metabolism data for UK Government Advisory Committee on Pesticides and its Subcommittee

- Member of PSD scientific assessment/review teams consisting of ecotoxicologists, toxicologists and residues/chemistry and efficacy assessors.
- Secretary of the Medical and Toxicology Panel of the Advisory Committee on Pesticides
- *Ad hoc* membership of other UK panels/committees: HSE Ad Hoc Bat Toxicity Working Group, Committee on Mutagenicity
- Toxicology Assessor for the World Health Organisation, Joint FAO/WHO Meeting on Pesticides Residues (1994 and 1995)
- Toxicology Advisor for the International Programme on Chemical Safety, Joint Meeting on Pesticides (1994)
- Management and training of other toxicologists

1987 – 1988 **Pesticides Safety Directorate:** Regulatory Scientist (Scientific Officer)

- General pesticides regulatory scientist

1984 - 1985 **ICI Plc, Environmental Laboratory:** Aquatic Toxicologist

- One year professional placement as part of BSc degree course: performed aquatic toxicity tests on marine and freshwater species in accordance with GLP, in order to assess the environmental hazards of a range of chemical substances

MEMBERSHIPS:

- Member of The Organisation for Professionals in Regulatory Affairs (TOPRA)
- Member of British Toxicology Society (BTS)

PUBLICATIONS/REPORTS:

- Author/Draft Author of human pharmaceutical pharmaco-toxicology expert reports/overviews (National, MRP, Centralised)
- Co-author of toxicology expert assessment for US FDA review
- Author of numerous toxicology and pharmacokinetic/metabolism sections of pesticide evaluations, published by the UK Government's Pesticides Safety Directorate
- Draft preparation of the toxicological evaluation of Teflubenzuron for the Joint FAO/WHO Meeting on Pesticides Residues (1994), published by WHO
- Draft preparation of the toxicological evaluation of Thiophanate-Methyl for the Joint FAO/WHO Meeting on Pesticides Residues (1995), published by WHO

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Education and Professional Qualifications:

- 1999 PhD (Herts) Agri-environmental Science; facilitating best practice in agriculture
- 1978 BSc (CNAA) Computer Science
- 1977 HND Chemistry

- Fellow of the Institute of Analysts and Programmers (FIAP)
- Associate Member of the Institute of Environmental Management and Assessment (IEMA)
- Member of the Society of Chemical Industry (SCI) – Active as a member of Pest Management Committee.
- Member of the Hertfordshire Rural Forum.

Employment History:

- **September 1994 – present:** Reader and Head of Agriculture and Environment Research Unit (AERU) Science and Technology Research Institute, University of Hertfordshire
- **March 1994 - September 1994:** Private consultancy work concerned with environmental management and software development. Contracted to University of Hertfordshire
- **March 1993 – March 1994:** Seconded to Texas Instruments Ltd, a major electronics company, acting as the sites environmental manager. Duties included Registration for IPC, introduction of BS7750, waste management and the identification and development of a clean-up strategy for the site's numerous pockets of contaminated land.
- **November 1972 – February 1993:** Warren Spring Laboratory (WSL), Department of Trade and Industry. Civil Service Grade Senior Scientific Officer. Deputy Manager of the Modelling, Software & Data Analysis Business Centre. Mainly responsible for environmental management, scientific software development and environmental data analysis (including odour modelling & assessment, fate and transport modelling of chemicals, assessing ammonia from livestock, mathematical modelling of mineral processing operations).

Personal Profile:

Dr Kathy Lewis is currently employed as a Reader and Head of the Agriculture and Environment Research Unit (AERU) within the Science and Technology Research Institute

(STRI), University of Hertfordshire. She has worked as a research scientist for over 33 years, with over 22 years at the DTI's environmental technology agency Warren Spring Laboratory (WSL) prior to its closure in 1994. In addition, she has experience in a wide range of associated environmental disciplines including fate and transport of pollutants in the environment, pesticide science, waste management, integrated water management and effluent treatment, air pollution and dispersion modelling, odour assessment, environmental auditing and impact assessments, contaminated land and EU & UK legislation.
Her research interests are broad covering all areas of environmental protection and defining and understanding best practice to minimise environmental damage. In particular:

- The fate, transport and ecotoxicity of pollutants into the environment.
- The interactions between agricultural, horticulture and the environment.

Kathy is currently working on several contract research projects. These include:

- Improving the best practice advice provided in farm assurance schemes to facilitate knowledge transfer and so improve practices. [Defra funded, 2005].
- Defining the sustainability of the UK strawberry crop [Defra funded, 2005]. This includes:
- environmental impact assessment of crop protection strategies, fertilisation programmes, input use (including energy and water) and waste/product management;
- economic assessment – farm and rural economies
- assessment of social acceptance and impacts on the quality of life.
- Improving energy efficiency of European Greenhouses. [EU Collective Research Programme, 2005]

Past projects have included:

- EU CAPER (EU Concerted Action on Pesticide Environmental Risk indicators). This project involves 15 EU states and sought to compare and contrast eight pesticide indicators of environmental toxicity.
- Development of a risk assessment approach for field evaluation of pesticides and other pollutants. This Defra funded research project developed a modelling approach for evaluating the fate, transport and ecotoxicity of agricultural pollutants.
- Life cycle sustainability (environmental impact, quality of life and economics) assessments of sugar beet from sowing to the retailer door.
- Ecotoxicological assessments of agricultural pesticides as part of a study to design an economic instrument for pesticide use in the UK. This project was funded by the DETR and carried out in collaboration with ECOTEC

Skills, abilities and experience

- Kathy has managed a comprehensive range of government and industry sponsored environmental projects.
- She has extensive management skills and is currently responsible for five full time staff members and a varying number of part time staff and placement students. She is also responsible for AERU project management and all finance. She is a fully trained PhD Student Supervisor.
- Kathy has written a significant number of scientific papers/reports and has presented many at major international conferences (publications list attached). In addition Kathy has refereed many scientific publications for leading journals and has done project evaluation work for the Environment Agency and European Commission.

- Extensive IT skills. Experienced in mathematical modelling of pollutants and database development. She has over 30 years computer programming experience (on and off-line) and is fluent in many software languages
- Kathy is a committee member of the SCI's national Pest Management Group and the expert environmental adviser to the Hertfordshire Rural Forum.
- In the past Kathy worked closely with UK and EC governments on environmental policy development including acting as the UK Governments representative to the 'Harmonisation of Sampling & Analysis of Waste' expert working group which was part of the International Bioenergy Agreement and had 28 member countries. Kathy was the appointed expert to the Herts CC Citizens Jury to develop the counties waste management strategy 1996. More recently she has collaborated and worked closely with some of the UK's major supermarkets, the British Agricultural Association, the European Crop Protection Association and the Fertilisers Manufacturers Association to promote and apply her research into environmental pollution arising from agriculture.

Examples of recent publications

- Environment Impact and Economic Assessment for UK Sugar Beet Production Systems (2004) Tzilivakis, J., Jaggard, K., Lewis, K. A., May, M. and Warner, D. J. Agriculture, Ecosystems and the environment. 107, 341-358
- Assessing the environmental impact of crop protection strategies for integrated farming systems (2004) J Tzilivakis, DB Turley, SE Ogilvy, KA Lewis and K Lawson, *Agronomie*. 24, pp67-76
- A prototype framework for assessing risks to soil functions (2004) J Tzilivakis, KA Lewis & A Williamson, *EIA Review*. Vol 25/2 pp 181-195
- p-EMA: evaluating ecological risks of agricultural chemicals for a farm-level risk assessment system. (2003) A Hart, KA Lewis and CD Brown *Agronomie*. 23, pp75-84
- p-EMA: simulating the environmental fate of agricultural chemicals for a farm-level risk assessment system. (2003) CD Brown, A Hart, KA Lewis and IG Dubus *Agronomie*. 23, pp67-74.
- P-EMA: overview and application of a software system designed to assess the environmental risks of agricultural chemicals. (2003) KA Lewis, CD Brown, A Hart, and J Tzilivakis. *Agronomie*. 23 pp85-96
- Comparison and evaluation of eight pesticide environmental risk indicators developed in Europe and recommendations for future use (2002). J Reus, P Leendertse, C Brockstaller, I Fomsgaard, V Gutsche, K Lewis, C Nilsson, L Pussemier, M Trevisan, H van der Werf, F Alfarroba, S Blumel, J Isart, D McGrath, T Seppala. *Agriculture, Ecosystems and Environment*. 90, 177-187
- Assessing the risks of agricultural pesticides at farm level. (2001) KA Lewis. OECD workshop on the economics of pesticide risk reduction in agriculture. Copenhagen, 28-30 November 2001. Invited presentation.
- Exposure assessment to support on-farm risk characterisation for pesticides. (2001) CD brown, KA Lewis and A hart. European meeting of the society of environmental toxicology and chemistry (SETAC). May 2001.

8.0 APPENDICES

8.1 CONFIDENTIAL APPENDICES

APPENDIX A: Measurement of K_{ow}
APPENDIX B: Measurement of ready biodegradation using modified Sturm test
APPENDIX C: Microbial respiration inhibition test
APPENDIX D: Freshwater algal growth inhibition test
APPENDIX E: *Daphnia magna* toxicity test

8.2 NON-CONFIDENTIAL APPENDICES

Not applicable

70 Page(s) Withheld

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_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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