Berichte

aus der Biologischen Bundesanstalt für Land- und Forstwirtschaft

Reports

from the Federal Biological Research Centre for Agriculture and Forestry

Heft 108

2002

EU-Beurteilungsbericht Cyclanilide

Rechtliche Regelungen der Europäischen Union zu Pflanzenschutzmitteln und deren Wirkstoffen

Band D 35

Review Report Cyclanilide
Legal Regulations of the European Union
for Plant Protection Products and their Active Substances
Volume D 35

Bearbeitet von
compiled by

Henning Bruno
Susanne Schaper

Abteilung für Pflanzenschutzmittel und Anwendungstechnik

Department of Plant Protection Products and Application Techniques

Herausgeber

Biologische Bundesanstalt für Land- und Forstwirtschaft
Braunschweig, Deutschland

Verlag
Eigenverlag

Vertrieb
Saphir-Verlag, Gutsstraße 15, D-38551 Ribbesbüttel
Telefon +49/(0) 53 74 / 65 76
Telefax +49/(0) 53 74 / 65 77

ISSN 0947-8809

Kontaktadresse
Dr. Henning Bruno
Biologische Bundesanstalt für Land- und Forstwirtschaft
Koordinierungsgruppe der Leitung der Abteilung für
Pflanzenschutzmittel und Anwendungstechnik
Messeweg 11/12
D-38104 Braunschweig

Telefon: +49/(0) 5 31 / 2 99-34 55
Telefax: +49/(0) 5 31 / 2 99-30 03
E-Mail: h.bruno@bba.de
Internet http://www.bba.de

Inhalt / Contents

Vorwort / Preface

Richtlinie 2001/87/EG der Kommission

Commission Directive 2001/87/EC

Review Report 7463/VI/98-final

Summary Report of the Meeting of the Standing Committee on Plant Health held on 29 June 2001

Opinion of the Scientific Committee on Plants, 14 December 2000

Bereits erschienene Beurteilungsberichte / Already published Review Reports

Heft / Report	**Band / Volume** **Wirkstoff / Active Substance**	**Berichterstattender Mitgliedstaat** **Rapporteur Member State**
59/2000	D1: Fluroxypyr	Deutschland Germany
60/2000	D2: Azimsulfuron	Italien Italy
61/2000	D3: Kresoxim-methyl	Belgien Belgium
65/2000	D4: Azoxystrobin	Deutschland Germany
66/2000	D5: Spiroxamine	Deutschland Germany
69/2000	D6: Imazalil	Luxemburg Luxembourg
70/2000	D7: Prohexadion-calcium	Frankreich France
71/2000	D8: Metsulfuron-methyl	Frankreich France
73/2001	D9: Esfenvalerat	Portugal Portugal
74/2001	D10: Bentazon	Deutschland Germany
75/2001	D11: Triasulfuron	Frankreich France
78/2001	D12: Lambda-Cyhalothrin	Schweden Sweden
79/2001	D13: Amitrol	Frankreich France
80/2001	D14: Deiquat	Vereinigtes Königreich United Kingdom
81/2001	D15: Pyridat	Österreich Austria
82/2001	D16: Chlozolinat	Griechenland Greece
83/2001	D17: Lindan	Österreich Austria
84/2001	D18: Monolinuron	Vereinigtes Königreich United Kingdom
85/2001	D19: Permethrin	Irland Ireland
86/2001	D20: Pyrazophos	Niederlande The Netherlands
87/2001	D21: Quintozen	Griechenland Greece
88/2001	D22: Tecnazen	Vereinigtes Königreich United Kingdom
89/2001	D23: Zineb	Italien Italy

Heft / Report	Band / Volume Wirkstoff / Active Substance	Berichterstattender Mitgliedstaat Rapporteur Member State
90/2001	D24: Thiabendazol	Spanien Spain
91/2001	D25: Fenhexamid	Vereinigtes Königreich United Kingdom
92/2001	D26: Glyphosat	Deutschland Germany
97/2002	D27: 2,4-D	Griechenland Greece
99/2002	D28: Thifensulfuron-methyl	Frankreich France
100/2002	D29: Flupyrsulfuron-methyl	Frankreich France
101/2002	D30: Paecilomyces fumosoroseus	Belgien Belgium
102/2002	D31: Isoproturon	Deutschland Germany
105/2002	D32: Acibenzolar-S-methyl	Frankreich France
106/2002	D33: Eisen(III)phosphat	Deutschland Germany
107/2002	D34: Ethofumesat	Schweden Sweden

Vorwort

Für neue Wirkstoffe werden die EU-Mitgliedstaaten in den Richtlinien zur Aufnahme der Wirkstoffe in Anhang I verpflichtet, den nach Abschluss aller Prüfungen erstellten Beurteilungsbericht (Review Report) mit allen Anlagen (mit Ausnahme von vertraulichen Informationen im Sinne von Artikel 14 der Richtlinie 91/414/EWG) allen Interessierten zur Verfügung zu stellen oder auf besonderen Antrag zugänglich zu machen. Für alte Wirkstoffe ergibt sich diese Verpflichtung für die Mitgliedstaaten bereits aus Artikel 7 Absatz 6 Unterabsatz 2 der Verordnung (EWG) Nr. 3600/92.

Die Mitgliedstaaten und die Europäische Kommission haben vereinbart, dass die Beurteilungsberichte, einschließlich der zum Teil sehr umfangreichen Hintergrunddokumente, vorzugsweise beim berichterstattenden Mitgliedstaat angefordert oder eingesehen werden sollen.

Die Biologische Bundesanstalt stellt die Beurteilungsberichte als Berichte aus der Biologischen Bundesanstalt für Land- und Forstwirtschaft als Band D in der Reihe "Rechtliche Regelungen der Europäischen Union zu Pflanzenschutzmitteln und deren Wirkstoffen" über den Saphir Verlag gegen Erstattung der Unkosten zur Verfügung. Das vorliegende 35. Heft dieser Reihe (Band D 35) enthält nicht die Hintergrunddokumente A, B und C des Beurteilungsberichtes. Diese können bei Bedarf bei der BBA eingesehen oder für die Wirkstoffe, für die Deutschland Berichterstatter ist, ebenfalls beim Saphir Verlag gegen Erstattung der Unkosten bezogen werden. Für Cyclanilide war Griechenland Berichterstatter.

In der Reihe "Rechtliche Regelungen der Europäischen Union zu Pflanzenschutzmitteln und deren Wirkstoffen" sind bisher erschienen:

Heft	**Rechtliche Regelungen der Europäischen Union zu Pflanzenschutzmitteln und deren Wirkstoffen**	
35/97	Band A:	Richtlinie 91/414/EWG und diesbezügliche Protokolle (3. Auflage, Stand: 01. November 1997) *wird zur Zeit bearbeitet*
68/2000	Band B:	Verordnungen und Protokolle zur Wirkstoffprüfung (4. Auflage, Stand 01. Juli 2000) *wird zur Zeit bearbeitet*
	Band C:	*wird zur Zeit bearbeitet*

Preface

According to the Directives for the inclusion of active substances in Annex I with regard to new active substances, EU-Member States are obliged to keep available or make available on special request the review report which is prepared after completion of all evaluations including its appendices (excluding confidential information, in accordance with article 14 of Directive 91/414/EEC) to all interested parties. For existing active substance this obligation for Member States already arises from article 7 (6) subparagraph 2 of Regulation (EEC) No 3600/92.

Member States and the European Commission agreed that requests of review reports including their background documents which are partly very voluminous, shall preferably be addressed to the Rapporteur Member State.

The Federal Biological Research Centre makes available review reports as reports from the Federal Biological Research Centre for Agriculture and Forestry, Volume D of the series "Legal Regulations of the European Union for Plant Protection Products and their Active Substances" via Saphir Verlag against reimbursement of expenses. The present 35th report belonging to this series (Volume D 35) does not include background documents A, B and C of the review report. If the need arises, their inspection at the BBA is possible or they may be also obtained from Saphir Verlag against reimbursement of expenses, however, only for active substances with Germany as Rapporteur Member State. For cyclanilide Greece acted as Rapporteur Member State.

In the series Legal Regulations of the European Union for Plant Protection Products and their Active Substances the following Reports have been published:

Report	**Legal Regulations of the European Union for Plant Protection Products and their Active Substances**	
35/97	Volume A:	Directive 91/414/EEC and respective Protocols (3rd Edition, date: 1 November 1997) *in progress*
68/2000	Volume B:	Regulations and Protocols regarding the Evaluation of Active Substances (4th Edition, date: 1 July 2000) *in progress*
	Volume C:	*in progress*

RICHTLINIE 2001/87/EG DER KOMMISSION

vom 12. Oktober 2001

zur Änderung des Anhangs I der Richtlinie 91/414/EWG des Rates über das Inverkehrbringen von Pflanzenschutzmitteln zur Aufnahme der Wirkstoffe Acibenzolar-s-methyl, Cyclanilide, Eisen(III)-phosphat, Pymetrozin und Pyraflufen-ethyl

DIE KOMMISSION DER EUROPÄISCHEN GEMEINSCHAFTEN —

gestützt auf den Vertrag zur Gründung der Europäischen Gemeinschaft,

gestützt auf die Richtlinie 91/414/EWG des Rates vom 15. Juli 1991 über das Inverkehrbringen von Pflanzenschutzmitteln [1], zuletzt geändert durch die Richtlinie 2001/49/EG der Kommission [2], insbesondere auf Artikel 6 Absatz 1,

in Erwägung nachstehender Gründe:

(1) Die Behörden Frankreichs haben am 15. Oktober 1996 gemäß Artikel 6 Absatz 2 der Richtlinie 91/414/EWG (im Folgenden „die Richtlinie" genannt) einen Antrag von Novartis — jetzt Syngenta — auf Aufnahme des Wirkstoffs Acibenzolar-s-methyl (CGA 245704) in Anhang I der Richtlinie erhalten. Mit der Entscheidung 97/865/EG der Kommission [3] wurde bestätigt, dass die Unterlagen „vollständig" sind und somit grundsätzlich die Anforderungen der Anhänge II und III der Richtlinie hinsichtlich der Daten und Informationen erfüllen.

(2) Die Behörden Griechenlands haben am 27. März 1996 einen Antrag von Rhône Poulenc Agrochimie SA (jetzt Aventis CropScience) für Cyclanilide (RPA 090946) erhalten. Dieser Antrag wurde mit der Entscheidung 97/137/EG der Kommission [4] für vollständig erklärt.

(3) Deutschland hat am 27. August 1998 einen Antrag von der W. Neudorff GmbH KG für Eisen(III)-phosphat erhalten. Dieser Antrag wurde mit der Entscheidung 1999/43/EG der Kommission [5] für vollständig erklärt.

(4) Deutschland hat darüber hinaus am 4. September 1996 einen Antrag von Novartis für Pymetrozin (CGA 215 944) erhalten. Dieser Antrag wurde mit der Entscheidung 97/865/EG für vollständig erklärt.

(5) Belgien hat am 16. Juni 1997 einen Antrag von Nihon Nohyaku Co. Ltd für Pyraflufen-ethyl erhalten. Dieser Antrag wurde mit der Entscheidung 98/242/EG der Kommission [6] für vollständig erklärt.

(6) Die Auswirkungen dieser fünf Wirkstoffe auf die menschliche Gesundheit und auf die Umwelt wurden gemäß Artikel 6 Absätze 2 und 4 der Richtlinie für die von dem jeweiligen Antragsteller vorgeschlagenen Anwendungen geprüft. Die Berichterstattenden Mitgliedstaaten haben der Kommission jeweils am 17. Dezember 1998 (Acibenzolar-s-methyl), 11. Februar 1998 (Cyclanilide), 30. Juli 1999 (Eisen(III)-phosphat), 28. Mai 1998 (Pymetrozin) und 8. Juli 1999 (Pyraflufen-ethyl) einen Entwurf des Bewertungsberichts über die Wirkstoffe übermittelt.

(7) Die Entwürfe der Bewertungsberichte wurden von den Mitgliedstaaten und der Kommission im Rahmen des Ständigen Ausschusses für Pflanzenschutz geprüft. Diese Prüfung wurde am 29. Juni 2001 in Form einzelner Beurteilungsberichte der Kommission für Acibenzolar-s-methyl, Cyclanilide, Eisen(III)-phosphat, Pymetrozin und Pyraflufen-ethyl abgeschlossen.

(8) Die Unterlagen und die aus den Prüfungen hervorgegangenen Informationen wurden dem Wissenschaftlichen Ausschuss „Pflanzen" übermittelt. Was Acibenzolar-s-methyl und Eisen(III)-phosphat angeht, so wurden dem Ausschuss keine besonderen Fragen vorgelegt. Der Ausschuss war der Auffassung, dass im Hinblick auf eine mögliche Aufnahme dieser Wirkstoffe in Anhang I der Richtlinie keine Anmerkungen zu machen sind [7]. Er wies darauf hin, dass dies nur als ein Hinweis darauf verstanden werden sollte, dass keine offensichtlichen Gründe für Anmerkungen vorliegen.

(9) In seiner Stellungnahme [8] über Cyclanilide hat der Ausschuss seine Auffassung hinsichtlich bestimmter Auswirkungen auf Mäuse und Kaninchen dargelegt und eine Neubewertung betreffend den Abbau des Bodenmetaboliten 2,4-Dichloranilin empfohlen. Die Empfehlungen des Ausschusses wurden berücksichtigt.

(10) In seiner Stellungnahme [9] über Pymetrozin hat der Ausschuss bestimmte Auswirkungen im Zusammenhang mit der Festlegung einer duldbaren täglichen Aufnahmemenge und einer akuten Referenzdosis für Verbraucher bewertet.

(11) In seiner Stellungnahme [10] über Pyraflufen-ethyl ist der Ausschuss zu dem Schluss gekommen, dass ein im Allgemeinen vernachlässigbares Risiko einer Grundwasserkontamination bei der Grundverbindung und ihren Abbauprodukten besteht. Unter extremen Bedingungen sollte jedoch der Verbleib bestimmter Abbauprodukte sorgfältig geprüft werden.

[1] ABl. L 230 vom 19.8.1991, S. 1.
[2] ABl. L 176 vom 29.6.2001, S. 61.
[3] ABl. L 351 vom 23.12.1997, S. 67.
[4] ABl. L 52 vom 22.2.1997, S. 20.
[5] ABl. L 14 vom 19.1.1999, S. 30.
[6] ABl. L 96 vom 28.3.1998, S. 45.

[7] Bericht über die Plenarsitzung des Wissenschaftlichen Ausschusses „Pflanzen" vom 7. März 2001 (Acibenzolar-s-methyl).
Bericht über die Plenarsitzung des Wissenschaftlichen Ausschusses „Pflanzen" vom 4. Juni 2001 (Eisen(III)-phosphat).

[8] Stellungnahme des Wissenschaftlichen Ausschusses „Pflanzen" hinsichtlich der Bewertung von Cyclanilide im Zusammenhang mit der Richtlinie 91/414/EWG über das Inverkehrbringen von Pflanzenschutzmitteln. SCP/CYCLAN/002-endg. vom 11. Dezember 2000.

[9] Stellungnahme des Wissenschaftlichen Ausschusses „Pflanzen" hinsichtlich der Bewertung von Pymetrozin im Zusammenhang mit der Richtlinie 91/414/EWG über das Inverkehrbringen von Pflanzenschutzmitteln. SCP/PYMETR/002-endg. vom 31. Januar 2001.

[10] Stellungnahme des Wissenschaftlichen Ausschusses „Pflanzen" hinsichtlich der Bewertung von Pyraflufen-ethyl im Zusammenhang mit der Richtlinie 91/414/EWG über das Inverkehrbringen von Pflanzenschutzmitteln. SCP/PYRA/-endg. vom 7 März 2001.

(12) Untersuchungen haben ergeben, dass davon ausgegangen werden kann, dass die betreffenden Wirkstoffe enthaltende Pflanzenschutzmittel im Allgemeinen die Anforderungen gemäß Artikel 5 Absatz 1 Buchstaben a) und b) und Absatz 3 der Richtlinie erfüllen, insbesondere hinsichtlich der geprüften und in den Beurteilungsberichten der Kommission behandelten Anwendungen. Daher sollten die betreffenden Wirkstoffe in Anhang I der Richtlinie aufgenommen werden, damit Pflanzenschutzmittel mit den betreffenden Wirkstoffen in allen Mitgliedstaaten gemäß den Bestimmungen der genannten Richtlinie zugelassen werden können.

(13) Nach der Aufnahme ist den Mitgliedstaaten eine angemessene Frist einzuräumen, um die Bestimmungen der Richtlinie über Pflanzenschutzmittel, die Acibenzolar-s-methyl, Cyclanilide, Eisen(III)-phosphat, Pymetrozin und Pyraflufen-ethyl enthalten, umzusetzen und insbesondere innerhalb dieser Frist bereits bestehende vorläufige Zulassungen zu überprüfen bzw. spätestens vor Ablauf der Frist neue Zulassungen gemäß der Richtlinie zu erteilen. Für Pflanzenschutzmittel, die einen der betreffenden Wirkstoffe und andere in Anhang I aufgeführte Wirkstoffe enthalten, kann auch eine längere Frist erforderlich sein.

(14) Der Beurteilungsbericht ist erforderlich für die ordnungsgemäße Umsetzung bestimmter Teile der einheitlichen Grundsätze gemäß Anhang VI der Richtlinie durch die Mitgliedstaaten, soweit sich diese Grundsätze auf die Bewertung der Angaben beziehen, die zwecks Aufnahme des Wirkstoffs in Anhang I der Richtlinie vorgelegt wurden. Es ist daher vorzuschreiben, dass die Mitgliedstaaten die endgültigen Beurteilungsberichte (mit Ausnahme von vertraulichen Informationen im Sinne des Artikels 14 der Richtlinie) allen Interessierten zur Einsicht zur Verfügung stellen oder zugänglich machen. Muss ein Beurteilungsbericht aktualisiert werden, um technischen und wissenschaftlichen Entwicklungen Rechnung zu tragen, so sollten die Bedingungen für die Aufnahme des betreffenden Wirkstoffs in Anhang I der Richtlinie in Übereinstimmung mit der Richtlinie ebenfalls geändert werden.

(15) Die in dieser Richtlinie vorgesehenen Maßnahmen entsprechen der Stellungnahme des Ständigen Ausschusses für Pflanzenschutz —

HAT FOLGENDE RICHTLINIE ERLASSEN:

Artikel 1

Die Tabelle in Anhang I der Richtlinie 91/414/EWG wird gemäß dem Anhang der vorliegenden Richtlinie geändert.

Artikel 2

(1) Die Mitgliedstaaten erlassen die erforderlichen Rechts- und Verwaltungsvorschriften, um dieser Richtlinie bis spätestens 31. März 2002 nachzukommen. Sie unterrichten die Kommission unverzüglich davon.

Bei Erlass dieser Vorschriften nehmen die Mitgliedstaaten in den Vorschriften selbst oder durch einen Hinweis bei der amtlichen Veröffentlichung auf diese Richtlinie Bezug. Die Mitgliedstaaten regeln die Einzelheiten der Bezugnahme.

(2) Hinsichtlich der Beurteilung und Entscheidungsfindung gemäß den einheitlichen Grundsätzen von Anhang VI der Richtlinie 91/414/EWG wird der in Absatz 1 festgesetzte Zeitraum jedoch auf der Grundlage von Unterlagen, die die Anforderungen von Anhang III derselben Richtlinie erfüllen, für vorläufige Zulassungen von Pflanzenschutzmitteln, die Acibenzolar-s-methyl, Cyclanilide, Eisen(III)-phosphat, Pymetrozin und Pyraflufen-ethyl enthalten, bis zum 31. März 2003 verlängert.

(3) Bei Pflanzenschutzmitteln, die Acibenzolar-s-methyl, Cyclanilide, Eisen(III)-phosphat, Pymetrozin oder Pyraflufen-ethyl zusammen mit einem anderen in Anhang I der Richtlinie 91/414/EWG aufgeführten Wirkstoff enthalten, wird der Zeitraum gemäß Absatz 1 jedoch insoweit verlängert, als die Vorschriften der Richtlinie über die Änderung des genannten Anhangs I eine längere Umsetzungsfrist vorsehen, um den Wirkstoff in den Anhang aufzunehmen.

(4) Die Mitgliedstaaten stellen die Beurteilungsberichte für Acibenzolar-s-methyl, Cyclanilide, Eisen(III)-phosphat, Pymetrozin und Pyraflufen-ethyl (mit Ausnahme von vertraulichen Informationen im Sinne des Artikels 14 der Richtlinie) allen Interessierten zur Einsicht zur Verfügung oder machen sie gegebenenfalls auf besonderen Antrag zugänglich.

Artikel 3

Diese Richtlinie tritt am 1. November 2001 in Kraft.

Artikel 4

Diese Richtlinie ist in alle Mitgliedstaaten gerichtet.

Brüssel, den 12. Oktober 2001

Für die Kommission

David BYRNE

Mitglied der Kommission

ANHANG

IN DIE TABELLE IN ANHANG I DER RICHTLINIE 91/414/EWG AUFZUNEHMENDE EINTRÄGE

Nr.	Gebräuchliche Bezeichnung, Kennnummern	IUPAC-Bezeichnung	Reinheit (1)	Inkrafttreten	Aufnahme befristet bis	Besondere Bedingungen
„20	Acibenzolar-s-methyl CAS Nr. 135158-54-2 CICAP Nr. 597	Benzo[1,2,3]tiadiazol-7-carbothioat-s-methyl	970 g/kg	1. November 2001	31. Oktober 2011	Nur Verwendungen als Pflanzenaktivator dürfen zugelassen werden Der Beurteilungsbericht wurde vom Ständigen Ausschuss für Pflanzenschutz am 29. Juni 2001 abgeschlossen
21	Cyclanilide CAS Nr. 113136-77-9 CICAP Nr. 586	Nicht verfügbar	960 g/kg	1. November 2001	31. Oktober 2011	Nur Verwendungen als Wachstumsregler dürfen zugelassen werden Der Höchstgehalt der Verunreinigung 2,4-Dichloroanilin (2,4-DCA) im hergestellten Wirkstoff sollte sich auf 1 g/kg belaufen Der Beurteilungsbericht wurde vom Ständigen Ausschuss für Pflanzenschutz am 29. Juni 2001 abgeschlossen
22	Eisen(III)-phosphat CAS Nr. 10045-86-0 CICAP Nr. 629	Eisen(III)-phosphat	990 g/kg	1. November 2001	31. Oktober 2011	Nur Verwendungen als Molluscizid dürfen zugelassen werden Der Beurteilungsbericht wurde vom Ständigen Ausschuss für Pflanzenschutz am 29. Juni 2001 abgeschlossen
23	Pymetrozin CAS Nr. 123312-89-0 CICAP Nr. 593	(*E*)-6-methyl-4-[(pyridin-3-ylmethylen)amino]-4,5-dihydro-2H-[1,2,4]-triazin-3-one	950 g/kg	1. November 2001	31. Oktober 2011	Nur Verwendungen als Insektizid dürfen zugelassen werden Bei der Entscheidungsfindung gemäß den einheitlichen Grundsätzen müssen die Mitgliedstaaten dem Schutz von Wasserorganismen besondere Aufmerksamkeit widmen Der Beurteilungsbericht wurde vom Ständigen Ausschuss für Pflanzenschutz am 29. Juni 2001 abgeschlossen

Nr.	Gebräuchliche Bezeichnung, Kennnummern	IUPAC-Bezeichnung	Reinheit (1)	Inkrafttreten	Aufnahme befristet bis	Besondere Bedingungen
24	Pyraflufen-ethyl CAS Nr. 129630-19-9 CICAP Nr. 605	Ethyl 2-chloro-5-(4-chloro-5-difluoromethoxy-1-methylpyrazol-3-yl)-4-fluorophenoxyacetat	956 g/kg	1. November 2001	31. Oktober 2011	Nur Verwendungen als Herbizid dürfen zugelassen werden Bei der Entscheidungsfindung gemäß den einheitlichen Grundsätzen müssen die Mitgliedstaaten dem Schutz von Algen und Wasserpflanzen besondere Aufmerksamkeit widmen und sollten gegebenenfalls Maßnahmen zur Risikominderung treffen Der Beurteilungsbericht wurde vom Ständigen Ausschuss für Pflanzenschutz am 29. Juni 2001 abgeschlossen

(1) Weitere Einzelheiten hinsichtlich der Identität und Spezifikation des Wirkstoffs sind dem Beurteilungsbericht zu entnehmen."

COMMISSION DIRECTIVE 2001/87/EC

of 12 October 2001

amending Annex I to Council Directive 91/414/EEC concerning the placing of plant protection products on the market to include acibenzolar-s-methyl, cyclanilide, ferric phosphate, pymetrozine and pyraflufen-ethyl as active substances

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Community,

Having regard to Council Directive 91/414/EEC of 15 July 1991 concerning the placing of plant protection products on the market [1], as last amended by Commission Directive 2001/49/EC [2], and in particular Article 6(1) thereof,

Whereas:

(1) In accordance with Article 6(2) of Directive 91/414/EEC (hereinafter referred to as 'the Directive') France received on 15 October 1996 an application from Novartis (now Syngenta) for the inclusion of the active subsrance acibenzolar-s-methyl (CGA 245704) in Annex I to the Directive. By Commission Decision 97/865/EC [3] it was confirmed that the dossier was 'complete' i.e. it could be considered as satisfying, in principle, the data and information requirements of Annex II and Annex III to the Directive.

(2) Greece received a similar application on 27 March 1996 from Rhône Poulenc Agrochimie SA (now Aventis CropScience), concerning cyclanilide (RPA 090946). This application was declared complete by Commission Decision 97/137/EC [4].

(3) On 27 August 1998, Germany received an application from W. Neudorff GmbH KG, concerning ferric phosphate. This application was declared complete by Commission Decision 1999/43/EC [5].

(4) Germany also received on 4 September 1996 an application from Novartis concerning pymetrozine (CGA 215944). By Commission Decision 97/865/EC this application was declared complete.

(5) On 16 June 1997, Belgium received an application from Nihon Nohyaku Co. Ltd, concerning pyraflufen-ethyl. This application was declared complete by Commission Decision 98/242/EC [6].

(6) For these five active substances, the effects on human health and the environment have been assessed, in accordance with the provisions of Article 6(2) and (4) of the Directive, for the uses proposed by the respective applicant. The nominated rapporteur Member States, submitted draft assessment reports concerning the substances to the Commission on 17 December 1998 (acibenzolar-s-methyl), 11 February 1998 (cyclanilide), 30 July 1999 (ferric phosphate), 28 May 1998 (pymethrozine) and 8 July 1999 (pyraflufen-ethyl), respectively.

(7) The draft assessment reports have been reviewed by the Member States and the Commission within the Standing Committee on Plant Health. The reviews were finalised on 29 June 2001 in the format of the individual Commission review reports for acibenzolar-s-methyl, cyclanilide, ferric phosphate, pymethrozine and pyraflufen-ethyl.

(8) The dossier and the information from each of the reviews were submitted to the Scientific Committee for Plants. As regards acibenzolar-s-methyl and ferric phosphate, no specific questions were addressed to the Committee. The Committee considered that there were no issues that it wished to raise regarding the active substances in the context of a possible inclusion in Annex I to the Directive [7]. The Committee noted that absence of comment should only be interpreted as an indication of no obvious reasons necessitating comment.

(9) In its opinion [8] concerning cyclanilide the Committee provided its interpretation of certain effects observed in mice and rabbits and recommended a reassessment of the degradation of the soil metabolite 2,4-dichloraniline. The recommendations of the Committee have been taken into consideration.

(10) In its opinion [9] on pymetrozine the Committee assessed certain effects in the context of deriving an acceptable daily intake and an acute reference dose for consumers.

(11) In its opinion [10] on pyraflufen-ethyl the Committee concluded that there is generally negligible risk of groundwater contamination for the parent compound and its breakdown products. However, under extreme conditions the fate of certain breakdown products should be assessed carefully.

[1] OJ L 230, 19.8.1991, p. 1.
[2] OJ L 176, 29.6.2001, p. 61.
[3] OJ L 351, 23.12.1997, p. 67.
[4] OJ L 52, 22.2.1997, p. 20.
[5] OJ L 14, 19.1.1999, p. 30.
[6] OJ L 96, 28.3.1998, p. 45.

[7] Minutes of the plenary meeting of the Scientific Committee for Plants from 7 March 2001 (acibenzolar-s-methyl).
Minutes of the plenary meeting of the Scientific Committee for Plants from 4 June 2001 (ferric phosphate).

[8] Opinion of the Scientific Committee for Plants regarding the evaluation of cyclanilide in the context of Directive 91/414/EEC concerning the placing of plant protection products on the market. SCP/CYCLAN/002-final dated 11 December 2000.

[9] Opinion of the Scientific Committee for Plants regarding the evaluation of pymetrozine in the context of Directive 91/414/EEC concerning the placing of plant protection products on the market. SCP/PYMETR/002-final dated 31 January 2001.

[10] Opinion of the Scientific Committee for Plants regarding the evaluation of pyraflufen-ethyl in the context of Directive 91/414/EEC concerning the placing of plant protection products on the market. SCP/PYRA/-final dated 7 March 2001.

(12) It has appeared from the various examinations made that plant protection products containing any of the active substances concerned may be expected to satisfy, in general, the requirements laid down in Article 5(1)(a), (b) and (3) of the Directive, in particular with regard to the uses which were examined and detailed in the respective Commission review reports. It is therefore appropriate to include these active substances in Annex I, in order to ensure that in all Member States the authorisations of plant protection products containing the active substances concerned can be granted in accordance with the provisions of the said Directive.

(13) After inclusion, a reasonable period is necessary to permit Member States to implement the provisions of the Directive on plant protection products containing acibenzolar-s-methyl, cyclanilide, ferric phosphate, pymetrozine or pyraflufen-ethyl and in particular to review, within this period, existing provisional authorisations or to grant, by the end of this period at the latest, new authorisations in accordance with the provisions of the Directive. A longer period may also be required for plant protection products containing any of the active substances concerned and other active substances included in Annex I.

(14) The review report is required for the proper implementation by the Member States, of several sections of the uniform principles laid down in Annex VI to the Directive, where those principles refer to the evaluation of the data which were submitted for the purpose of the inclusion of the active substance in Annex I to the Directive. It is, therefore, appropriate to provide that the finalised review reports (except for confidential information in the meaning of Article 14 of the Directive) are kept available or made available by the Member States for consultation by any interested parties. If a review report has to be updated to take account of technical and scientific developments, the conditions for the inclusion of the active substance concerned in Annex I to the Directive should also be amended in accordance with the Directive.

(15) The measures provided for in this Directive are in accordance with the opinion of the Standing Committee on Plant Health,

HAS ADOPTED THIS DIRECTIVE:

Article 1

The table in Annex I to Directive 91/414/EEC shall be amended as set out in the Annex hereto.

Article 2

1. Member States shall bring into force the laws, regulations and administrative provisions necessary to comply with this Directive, at the latest by 31 March 2002. They shall forthwith inform the Commission thereof.

When Member States adopt those provisions, they shall contain a reference to this Directive or shall be accompanied by such a reference on the occasion of their official publication. Member States shall determine how such reference is to be made.

2. However, with regard to evaluation and decision-making pursuant to the uniform principles provided for in Annex VI to Directive 91/414/EEC, on the basis of a dossier satisfying the requirements of Annex III thereto, the period laid down in the first paragraph is extended for existing provisional authorisations of plant protection products containing acibenzolar-s-methyl, cyclanilide, ferric phosphate, pymetrozine or pyraflufen-ethyl to 31 March 2003.

3. However for plant protection products containing acibenzolar-s-methyl, cyclanilide, ferric phosphate, pymetrozine or pyraflufen-ethyl together with another active substance which is in Annex I to Directive 91/414/EEC, the period referred to in paragraph 1 is extended to the extent that a longer implementation period is provided for by the provisions laid down in the Directive amending Annex I to Directive 91/414/EEC to include the substance in the Annex.

4. Member States shall keep available the review reports for acibenzolar-s-methyl, cyclanilide, ferric phosphate, pymetrozine and pyraflufen-ethyl (except for confidential information within the meaning of Article 14 of the Directive) for consultation by any interested parties or shall make it available to them on specific request.

Article 3

This Directive shall enter into force on 1 November 2001.

Article 4

This Directive is addressed to the Member States.

Done at Brussels, 12 October 2001.

For the Commission

David BYRNE

Member of the Commission

ANNEX

ENTRIES TO BE INSERTED IN THE TABLE IN ANNEX I TO DIRECTIVE 91/414/EEC

No	Common name, identification numbers	IUPAC name	Purity (1)	Entry into force	Expiration of inclusion	Specific provisions
'20	Acibenzolar-s-methyl CAS No 135158-54-2 CIPAC No 597	Benzo[1,2,3]thiadiazole-7-carbothioic acid S-methyl ester	970 g/kg	1 November 2001	31 October 2011	Only uses as a plant activator may be authorised. Date of Standing Committee on Plant Health at which the review report was finalised: 29 June 2001.
21	Cyclanilide CAS No 113136-77-9 CIPAC No 586	Not available	960 g/kg	1 November 2001	31 October 2011	Only uses as a plant growth regulator may be authorised. The maximum content of the impurity 2,4-dichloroaniline (2,4-DCA) in the active substance as manufactured should be 1 g/kg. Date of Standing Committee on Plant Health at which the review report was finalised: 29 June 2001.
22	Ferric phosphate CAS No 10045-86-0 CIPAC No 629	Ferric phosphate	990 g/kg	1 November 2001	31 October 2011	Only uses as a molluscicide may be authorised. Date of Standing Committee on Plant Health at which the review report was finalised: 29 June 2001
23	Pymetrozine CAS No 123312-89-0 CIPAC No 593	(E)-6-methyl-4-[(pyridin-3-ylmetylene)amino]-4,5-dihydro-2H-[1,2,4]-triazin-3 one	950 g/kg	1 November 2001	31 October 2011	Only uses as an insecticide may be authorised. In decision-making according to the uniform principles Member States must pay particular attention to the protection of aquatic organisms. Date of Standing Committee on Plant Health at which the review report was finalised: 29 June 2001.

No	Common name, identification numbers	IUPAC name	Purity (1)	Entry into force	Expiration of inclusion	Specific provisions
24	Pyraflufen-ethyl CAS No 129630-19-9 CIPAC No 605	Ethyl-2-chloro-5-(4-chloro-5-difluoromethoxy-1-mhypyrazol-3-yl)-4-fluorophenoxyacetate	956 g/kg	1 November 2001	31 October 2011	Only uses as a herbicide may be authorised. In decision-making according to the uniform principles Member States must pay particular attention to the protection of algae and aquatic plants and should apply, where appropriate, risk mitigation measures. Date of Standing Committee on Plant Health at which the review report was finalised: 29 June 2001.

(1) Further details on identity and specification of active substances are provided in the review report.'

EUROPEAN COMMISSION
DIRECTORATE-GENERAL HEALTH & CONSUMER PROTECTION

Directorate E - Public, animal and plant health
Unit E1 Legislation relating to crop products and animal nutrition

Cyclanilide

7463/VI/98-final

12 December 2001

COMMISSION WORKING DOCUMENT - DOES NOT NECESSARILY REPRESENT THE VIEWS OF THE COMMISSION SERVICES

Review report for the active substance **cyclanilide**

Finalised in the Standing Committee on Plant Health at its meeting on 29 June 2001 in view of the inclusion of cyclanilide in Annex I of Directive 91/414/EEC.

1. Procedure followed for the evaluation process

This review report has been established as a result of the evaluation of the new active substance cyclanilide, made in the context of the work provided for in Articles 5 and 6 of Directive 91/414/EEC concerning the placing of plant protection products on the market, with a view to the possible inclusion of this substance in Annex I to the Directive.

In accordance with the provisions of Article 6(2) of Directive 91/414/EEC, the Greek authorities received on 27 March 1996 an application from Rhône-Poulenc Agrochimie S.A.(now known as AVENTIS CropScience), hereafter referred to as the applicant, for the inclusion of the active substance RPA 090946 (cyclanilide) in Annex I to the Directive. Greek authorities indicated to the Commission on 30 May 1996 the results of a first examination of the completeness of the dossier, with regard to the data and information requirements provided for in Annex II and, for at least one plant protection product containing the active substance concerned, in Annex III to the Directive. Subsequently, and in accordance with the requirements of Article 6(2), a dossier on cyclanilide was distributed to the Member States and the Commission.

The Commission referred the dossier to the Standing Committee on Plant Health in the meeting of the working group 'legislation' thereof on 14 June 1996, during which the Member States confirmed the receipt of the dossier.

In accordance with the provisions of Article 6(3), which requires the confirmation at Community level that the dossier is to be considered as satisfying, in principle, the data and information requirements provided for in Annex II and, for at least one plant protection product containing the active substance concerned, in Annex III to the Directive and in accordance with

the procedure laid down in Article 20 of the Directive, the Commission confirmed in its Decision 97/137[1] of 3 February 1997 that these requirements were satisfied.

Within the framework of that decision and with a view to the further organisation of the works related to the detailed examination of the dossier provided for in Article 6(2) and (4) of Directive 91/414/EEC, it was agreed between the Member States and the Commission that Greece would, as rapporteur Member State, carry out the detailed examination of the dossier and report the conclusions of its examination accompanied by any recommendations on the inclusion or non-inclusion and any conditions relating thereto, to the Commission as soon as possible and at the latest within a period of one year.

Greece submitted to the Commission on 11 February 1998 the report of its detailed scientific examination, hereafter referred to as the draft assessment report, including, as required, a recommendation concerning the possible inclusion of cyclanilide in Annex I to the Directive.

On receipt of the draft assessment report, the Commission forwarded it for consultation to all the Member States on 23 June 1998 as well as to the applicant on 30 June 1998.

The Commission organised further an intensive consultation of specialised scientific experts from a representative number of Member States, to review the draft assessment report and the comments received thereon (peer review), in particular on each of the following disciplines :

- identity and physical /chemical properties ;
- fate and behaviour in the environment ;
- ecotoxicology ;
- mammalian toxicology ;
- residues and analytical methods ;
- regulatory questions.

The meetings for this consultation were organised on behalf of the Commission by the Pesticide Safety Directorate (PSD) in York, United Kingdom, from September 1998 to January 1999.

The report of the peer review (i.e. full report) was circulated, for further consultation, to Member States and the sole applicant on 18 May 1999.

The dossier, draft assessment report and the peer review report (i.e. full report) including in particular an outline resumé of the remaining technical questions, were referred to the Standing Committee on Plant Health, and specialised working groups of this Committee, for final examination, with participation of experts from the 15 Member States. This final examination took place from September 1999 to June 2001, and was finalised in the meeting of the Standing Committee on 29 June 2001.

The present review report contains the conclusions of this final examination; given the importance of the draft assessment report, the peer review report (i.e. full report) and the comments and clarifications submitted after the peer review as basic information for the final examination process, these documents are considered respectively as background documents A, B and C to this review report and are part of it.

[1] OJ No L52, 22.02.1997, p.20.

These documents were also submitted to the Scientific Committee for Plants for separate consultation. With regard to certain effects of cyclanilide on the thymus and spleen of mice, the SCP did not consider these effects to indicate a specific immunotoxicity of the substance. These effects were considered to represent an unspecific response to stress following exposure to very high levels of the active substance. Also the results of the developmental toxicity study in rabbits were not regarded as indicative of reproductive toxicity potential of cyclanilide to humans. The reported findings were only observed in the top-dose animals showing salient signs of systemic toxic effects and no similar effects on reproduction were seen in other studies for reproductive toxicity. The report of this Committee was formally adopted on 30 November 2000[2].

2. Purposes of this review report

This review report, including the background documents and appendices thereto, have been developed and finalised in support of the Directive 2001/87/EC concerning the inclusion of cyclanilide in Annex I to Directive 91/414/EEC, and to assist the Member States in decisions on individual plant protection products containing cyclanilide they have to take in accordance with the provisions of that Directive, and in particular the provisions of article 4(1) and the uniform principles laid down in Annex VI.

This review report provides also for the evaluation required under Section A.2.(b) of the above mentioned uniform principles, as well as under several specific sections of part B of these principles. In these sections it is provided that Member States, in evaluating applications and granting authorisations, shall take into account the information concerning the active substance in Annex II of the directive, submitted for the purpose of inclusion of the active substance in Annex I, as well as the result of the evaluation of those data.

In parallel with the provisions of Article 7(6) of Regulation 3600/92 for existing active substances, the Commission and the Member States will keep available or make available this review report for consultation by any interested parties or will make it available to them on their specific request. Moreover the Commission will send a copy of this review report (not including the background documents) to the applicant.

The information in this review report is, at least partly, based on information, which is confidential and/or protected under the provisions of Directive 91/414/EEC. It is therefore recommended that this review report would not be accepted to support any registration outside the context of Directive 91/414/EEC, e.g. in third countries, for which the applicant has not demonstrated possession of regulatory access to the information on which this review report is based.

3. Overall conclusion in the context of Directive 91/414/EEC

The overall conclusion from the evaluation is that it may be expected that plant protection products containing cyclanilide will fulfil the safety requirements laid down in Article 5(1)(a) and (b) of Directive 91/414/EEC. This conclusion is however subject to compliance with the particular requirements in sections 4, 5, 6 and 7 of this report, as well as to the implementation of the provisions of Article 4(1) and the uniform principles laid down in Annex VI of Directive 91/414/EEC, for each cyclanilide containing plant protection product for which Member States will grant or review the authorisation.

---

[2] Opinion of the Scientific Committee on Plants regarding the inclusion of cyclanilide in Annex I to Council Directive 91/414/EEC concerning the placing of plant protection products on the market. (Opinion adopted by the Scientific Committee on Plants on 30 November 2000)

Furthermore, these conclusions were reached within the framework of the following use, which was proposed and supported by the notifier:

- plant growth regulator for use in cotton

Extension of the use pattern beyond that described above will require an evaluation at Member State level in order to establish whether the proposed extensions of use can satisfy the requirements of Article 4(1) and of the uniform principles laid down in Annex VI of Directive 91/414/EEC.

4. Specific conclusions which are highlighted in this evaluation

4.1 Residues of cyclanilide in foodstuffs

The review has established that the residues arising from the proposed uses, consequent on application consistent with good plant protection practice, have no harmful effects on human or animal health. The Theoretical Maximum Daily Intake (TMDI) for a 60 kg adult is 2.7 % of the Acceptable Daily Intake (ADI) of 0.0075 mg/kg b.w./day, based on the FAO/WHO European Diet (August 1994). This low intake value reflects the current limited use pattern for this active substance. The highest National (UK) estimates of short term intake (NESTI) for toddlers is 0.0006 mg/kg b.w./ day, which corresponds to 4% of the Acute Reference Dose (aRfD) of 0.015 mg/kg b.w./day.

4.2 Exposure of operators, workers and bystanders

The review has identified acceptable exposure scenarios for operators, workers and bystanders, which require, however, confirmation for each plant protection product in accordance with the relevant sections of the above mentioned uniform principles.

4.3 Ecotoxicology

The review has concluded that the proposed use has no unacceptable effects on the environment, as provided for in Article 4 (1) (b) (iv) and (v) of Directive 91/414/EEC.

5. Identity and Physical/chemical properties

The identity and the main physical/chemical properties of cyclanilide are given in Appendix I.

The active substance shall have a minimum purity of 960 g/kg technical product.

The review has established that for the active substance notified by the applicant Rhône-Poulenc Agrochimie S.A. (now known as Aventis CropScience), the manufacturing impurity 2,4 dicloroaniline (2,4 DCA) is of toxicological concern and the maximum content in the active substance as manufactured should be not higher than 1 g/kg.

6. Endpoints and related information

In order to facilitate Member States, in granting or reviewing authorisations, to apply adequately the provisions of Article 4(1) of Directive 91/414/EEC and the uniform principles laid down in Annex VI of that Directive, the most important endpoints as identified during the evaluation process are listed in Appendix II.

7. Particular conditions to be taken into account on short term basis by Member States in relation to the granting of authorisations of plant protection products containing cyclanilide

On the basis of the proposed and supported use, no particular issues have been identified which would require short term attention from the Member States, in the framework of any authorisations to be granted, varied or withdrawn, as appropriate.

8. List of studies to be generated

No further studies were identified which were considered at this stage, and under the current inclusion conditions necessary in relation to the inclusion of cyclanilide in Annex I.

9. Information on studies with claimed data protection

For information of any interested parties, Appendix III gives information about the studies for which the applicant has claimed data protection and which are not present in the original dossier neither mentioned in the monograph. This information is only given to facilitate the operation of the provisions of Article 13 of Directive 91/414/EEC in the Member States. It is based on the best information available to the Commission services at the time this review report was prepared; but it does not prejudice any rights or obligations of Member States or operators with regard to its uses in the implementation of the provisions of Article 13 of the Directive 91/414/EEC neither does it commit the Commission.

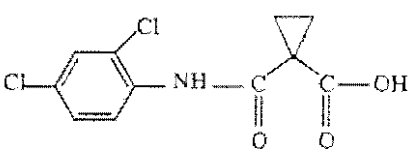
10. Updating of this review report

The technical information in this report may require periodic updating to take account of technical and scientific developments as well as of the results of the examination of any information referred to the Commission in the framework of Articles 7, 10 or 11 of Directive 91/414/EEC. Such adaptations will be examined and finalised in the Standing Committee on Plant Health, in connection with any amendment of the inclusion conditions for cyclanilide in Annex I of the Directive.

APPENDIX I

Identity, physical and chemical properties

CYCLANILIDE

Common name (ISO)	Cyclanilide
Chemical name (IUPAC)	Not available
Chemical name (CA)	1-(2,4-dichlorophenylaminocarbonyl)-cyclopropane carboxylic acid
CIPAC No	586
CAS No	113136-77-9
EEC No	Not yet assigned
FAO SPECIFICATION	Not yet assigned
Minimum purity	960 g/kg
Identity of relevant impurities of toxicological significance in the active substance as manufactured (g/kg)	2,4-dichloroaniline max 1 g/kg
Molecular formula	$C_{11}H_9Cl_2NO_3$
Molecular mass	274.1
Structural formula	

Melting point	195 °C (purity 99.2 %), 196 °C (purity 99.0 %)
Boiling point	Not relevant
Appearance	Pure active substance: no data Technical active substance (purity 99 %): white powdery solid with no characteristic odour
Relative density	1.482 g/ml at 20 °C (purity 99.2 %) 1.469 g/ml at 20 °C (purity 99.0 %)
Vapour pressure	$0.84 \cdot 10^{-5}$ Pa at 50 °C (purity 99.0 %) Estimated < $1.33 \cdot 10^{-5}$ Pa at 25 °C
Henry's law constant	< $7.41 \cdot 10^{-5}$ Pa·m^3·mol^{-1} at 20 °C (It was calculated using the vapour pressure value of < 10^{-5} Pa and the 0.037 g/l water solubility value)
Solubility in water	At 20 °C, purity 99.2 %: pH 5.2 (distilled water): 0.037 g/l pH 7: 0.048 g/l pH 9: 0.048 g/l
Solubility in organic solvents	At 20 °C: hexane: < 0.001 g/l toluene: 0.6 g/l dichloromethane: 1.7 g/l methanol: 59.1 g/l octanol-1: 67.2 g/l propanol-2: 68.2 g/l acetone: 52.9 g/l ethyl acetate: 31.8 g/l acetonitrile: 5.0 g/l
Partition co-efficient (log P_{OW})	Distilled water (pH not stated): log P_{ow}= 3.25 at 21 °C (purity 99.4%)
Hydrolytic stability (DT_{50})	pH 5, 7 and 9: Not hydrolysed at 25 °C
Dissociation constant	pKa: 3.5
Quantum yield of direct photo-transformation in water at ε >290 nm	Quantum yield at 305 nm: 4.26×10^{-3}
Flammability	Not highly flammable
Explosive properties	Non-explosive
UV/VIS absorption (max.)	λ_{max} : 211.0 nm, 256.0 nm ε ($M^{-1} \cdot cm^{-1}$): ε_{211}= 29840, ε_{256}= 21249 At 290 nm. ε=1215 $M^{-1} \cdot cm^{-1}$

Photostability (DT_{50})	pH 5: 997 h under xenon lamp equivalent to 49.9 summer days in Florida pH 7: 1173 h under xenon lamp equivalent to 55.1 summer days in Florida pH 9: 995 h under xenon lamp equivalent to 53.7 summer days in Florida

APPENDIX II

END POINTS AND RELATED INFORMATION

CYCLANILIDE

1 Toxicology and metabolism

Absorption, distribution, excretion and metabolism in mammals

Rate and extent of absorption:	Rapid, Tmax approximately 1 h, minimum 62 % absorbed at low dose.
Distribution:	Highest concentration skin and fur, lower in liver and kidney after 7 days.
Potential for accumulation:	Low potential for body accumulation.
Rate and extent of excretion:	Higher than 90 % elimination at 48 hrs mainly via urine at low dose.
Toxicologically significant compounds:	Parent compound, 2,4-DCA. Less extensive metabolism in farm animals
Metabolism in animals:	Approximately 90 % metabolised mainly to methyl ester and amino acid conjugates (at least 32 fractions).

Acute toxicity

Rat LD_{50} oral:	208 mg/kg bw
Rat LD_{50} dermal:	> 2000 mg/kg bw
Rat LC_{50} inhalation:	> 5.15 mg/l, nose only exposure
Skin irritation:	Non-irritant
Eye irritation:	Non-irritant
Skin sensitization (test method used and result)	Not sensitising (M&K maximisation test, result: negative)

Short term toxicity

Target / critical effect:	Liver and ovaries
Lowest relevant oral NOAEL/NOEL	4.2 mg/kg b.w./day (160 ppm), 1 year dog study
Lowest relevant dermal NOAEL	1000 mg/kg bw/d
Lowest relevant inhalation NOAEL/NOEL	No data required

Genotoxicity

Evidence of clastogenic potential *in vitro*. No evidence of genotoxicity in the micronucleus test. No evidence of UDS induction *in vivo*.

Long term toxicity and carcinogenicity

Target / critical effect:	Liver
Lowest relevant NOAEL:	5 mg/kg bw/d (150 ppm), 2 year rat study
Carcinogenicity:	No carcinogenic potential

Reproductive toxicity

Target / critical effect – Reproduction:	Decreased pup weight and number of implantation sites at parental toxic doses.
Lowest relevant reproductive NOAEL/NOEL:	LOEL of 1.5 mg/kg bw/d (30 ppm) due to renal calculi at this dose in F1.
Developmental target / critical effect:	Embryo-feto toxicity at maternally toxic doses.
Lowest relevant developmental NOAEL:	Below 3 mg/kg bw/d, rabbits.

Delayed neurotoxicity

NOEL subchronic = 2.5 mg/kg bw/d (50 ppm) based on increased motor activity in the rat

Other toxicological studies

Acute neurotoxicity NOEL = 50 mg/kg bw/d

Medical data

Cnrrently limited: new active substance. No detrimental effects in manufacturing or development personnel.

Summary

	Value	Study	Safety factor
ADI:	0.0075 mg/kg bw/day	2-generation rat reproductive study	200
AOEL systemic	0.0045 mg/kg bw/day	2-generation rat reproduction study (60 % oral absorbtion)	200
AOEL inhalation	not required		
AOEL dermal	not required		
ARfD (acute reference dose):	0.015 mg/kg bw/day	Rabbit developmental toxicity study	200

Dermal absorption

10% default value used.

2 Fate and behaviour in the environment

2.1 Fate and behaviour in soil

Route of degradation

Aerobic:

Mineralization after 100 days:	at day 120 : 4.3 % of CO_2 at day 180 : 24.5 % of CO_2
Non-extractable residues after 100 days:	at day 120 : 30 % of bound residues
Relevant metabolites above 10 % of applied active substance: name and/or code % of applied rate (range and maximum)	2,4-Dichloroaniline (2,4-DCA): 1.5 - 16% of applied radioactivity (A.R.) maximum of 2,4-DCA at day 30: 16 % of A.R.

Supplemental studies

Anaerobic:	Practically cyclanilide is not degradable.
Soil photolysis:	DT_{50} at 25.4 °C : 151 days
Remarks:	None

Rate of degradation

Laboratory studies

Method of calculation	a : non-linear analysis (Gustafson and Holden, 1990) b : first order kinetics
DT_{50}lab (20 °C, aerobic):	20°C, aerobic: 15 - 49 days (b, n=3, R^2=0.99) mean : 29 d. 25±1°C, aerobic: 16 - 62 days (a, n=2, R^2=0.76 - 0.90) mean : 39 d.
DT_{50}lab (25°C, aerobic) 2,4-dichloroaniline (2,4-DCA)	DT_{50}lab, 25°C, aerobic: 65.6 – 78.5 days (b, n=2, R^2= 0.983 – 0.996) mean : 72 d.
DT_{90}lab (20 °C, aerobic):	50 - 162 days (b, n=3, R^2=0.99) mean : 96 d.
DT_{50}lab (10 °C, aerobic):	not required
DT_{50}lab (20 °C, anaerobic):	≥ 15 months (b, n=1)

Field studies (country or region)

DT_{50f} from soil dissipation studies:	11 - 45 d (S.France and Spain, b, n=2, R^2=0.76-0.85) mean : 28 d. 34 - 114 d (Mississippi, N.Carolina, California, Texas, b, n=4, R^2=0.66-0.93) mean : 65 d.
DT_{90f} from soil dissipation studies:	37 - 151 d (S.France and Spain, b, n=2, R^2=0.76-0.85) mean : 94 d.
Soil accumulation studies:	No data are required.
Soil residue studies:	not required

Remarks: e.g. effect of soil pH on degradation rate	None

Adsorption/desorption

K_f / K_{OC}:	K_{oc}: cyclanilide 304 194 565 367 300 SL LS SiL C pond sediment K_{oc} : 2,4-DCA) 349 492 681 513 883 SL LS SiL C pond sediment
K_d	1.05 - 3.83 for cyclanilide and 1.28 - 21.8 for 2,4-DCA
pH dependence:	Yes (Koc value decreases when pH increases)

Mobility

Laboratory studies:

Column leaching:	No data are required.
Aged residue leaching:	Cyclanilide in the leachate : 0.36 - 2.64 % of A.R.

Field studies:

Lysimeter/Field leaching studies:	No data are required.
Remarks:	None

2.2 Fate and behaviour in water

Abiotic degradation

Hydrolytic degradation:	No degradation for the pH values 5, 7 and 9 tested.
Relevant metabolites	no metabolite found above 10% of A.R.
Photolytic degradation:	DT_{50} (summer days in Florida): 49.9 days 55.1 days 53.7 days pH 5 pH 7 pH 9
Relevant metabolites	no metabolite found above 10% of A.R.

Biological degradation

Readily biodegradable:	No data are required.
Water/sediment study:	River (Mumpf) Pond (Anwil)
DT_{50} water:	18 days 17 days
DT_{90} water:	201 days 157 days
DT_{50} whole system:	63 days 56 days
DT_{90} whole system:	208 days 185 days
	DT_{50} sediment(2,4-dichloroaniline) 78 days 45 days
Distribution in water / sediment systems (active substance)	water phase : 41 - 45% at day 28 14 - 18% at day 105 sediment : 29 - 37% at day 28 13 - 15% at day 105
Distribution in water / sediment systems (2,4-dichloroaniline)	water phase :max. of 0.5% at one time point sediment : 12 - 15% at day 56 and 10 - 11% at day 105
Mineralization	5 - 7% CO2 at day 105
Non-extractable residues	sediment : 27 - 31% at day 105
Accumulation in water and/or sediment:	not required

Degradation in the saturated zone

	No data are required.
Remarks:	None

2.3 Fate and behaviour in air

Volatility

Vapour pressure:	$0.84 \cdot 10^{-5}$ Pa at 50 °C (purity 99.0 %) Estimated $<1.33 \cdot 10^{-5}$ Pa at 25 °C
Henry's law constant:	$< 7.41 \cdot 10^{-5}$ Pa·m^3·mol^{-1} at 20 °C (It was calculated using the vapour pressure value of $< 10^{-5}$ Pa and the 0.037 g/l water solubility value.)

Photolytic degradation

Direct photolysis in air:	Not required.
Photochemical oxidative degradation in air DT_{50}:	DT_{50} : 8 daylight hours (Atkinson method)

Volatilisation

	From plant surfaces: not volatilized in 24-hour period. From soil: not volatilized from soil
Quantum yield of direct phototransformation	not required

Remarks:	None

3 Ecotoxicology

Terrestrial Vertebrates

Acute toxicity to mammals:	> 5000 mg as/kg bw
Acute toxicity to birds:	> 216 mg as/kg bw
Dietary toxicity to birds:	> 1240 mg as/kg
Reproductive toxicity to birds:	Not required due to minimal risk.
Short term oral toxicity to mammals:	160 ppm, 1 year dog study

Aquatic Organisms

Acute toxicity fish:	LC_{50} = 11 mg as/l (*O. mykiss*, short term)
Long term toxicity fish	NOEC = 2.6 mg as/l (*P. promelas*)
Bioaccumulation fish:	Distilled water (pH not stated): log Pow= 3.25 at 21 oC (purity 99.4%) – BCF: 0.36, no bioaccumulation is anticipated.
Acute toxicity invertebrate:	EC_{50}= 13 mg as/l (*D. magna*, short term)
Chronic toxicity invertebrate:	NOEC = 12.6 mg as/l (*D. magna*)
Acute toxicity algae:	EC_{50}(cell density)= 1.7 mg as/l (*S. capricornutum*, short term)
Chronic toxicity sediment dwelling organism:	NOEC = >0.5 mg 2,4-Dichloroaniline/l (*C. riparius*, long term)
Toxicity aquatic plants:	EC_{50} => 0.22 mg/l & NOEC = 0.22 mg/l

Honeybees

Acute oral toxicity:	LD 50: 89.5 µg as/bee
Acute contact toxicity:	LD 50: > 100 µg as/bee

Other arthropod species

Orius insidiosus	Survival and reproduction of nymphs and adults (stage: nymphs; EXP 31039C: 4.05 kg ~~as~~/ha – formulation contains 480 g/l ethephon and 60 g/l cyclanilide): 1.9% overall survival & reproduction; 17% nymphal mortality; 22% mortality of nymphs and adults
T. pyri	Mortality of protonymphs (stage:14 d old; EXP 31039C: 4.05 kg ~~as~~/ha– formulation contains 480 g/l ethephon and 60 g/l cyclanilide): 100%
Pardosa sp.	Mortality behaviour and feeding rate (stage:14 d old; EXP 31039C: 4.05 kg ~~as~~/ha– formulation contains 480 g/l ethephon and 60 g/l cyclanilide): No effect
A. rhopalosiphi	Mortality (stage:parastitisation; EXP 31039C:4.05 kg ~~as~~/ha– formulation contains 480 g/l ethephon and 60 g/l cyclanilide): 100%
A. rhopalosiphi	Extended Laboratory Test: Mortality, behaviour & parasitization rate (stage:adult parasitisation: 3 l EXP 31039C /ha– formulation contains 480 g/l ethephon and 60 g/l cyclanilide): Beneficial capacity: 7.1% effect

Earthworms

Acute toxicity:	469 mg as/kg d. wt. soil > 1000 mg /kg d. wt. soil (formulation)
Reproductive toxicity:	Not available

Soil micro-organisms

Nitrogen mineralization:	By 28 days of exposure the effect on all processes was less than 15% at either application rate.
Carbon mineralization:	By 28 days of exposure the effect on all processes was less than 15% at either application rate.

Appendix III

CYCLANILIDE

List of studies which were submitted during the evaluation process and were not cited in the draft assessment report:

B.1 Identity

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Date of submission
IIA, 1.9, 1.10, 1.11	Cousin, J:	1996	Technical Cyclanilide Analysis and certification of product ingredients Rhône-Poulenc Agro Report/file N°: R&D/CRLD/AN/9615841 GLP or GEP: yes Published: no	1998

B.2 Physical and chemical properties

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Date of submission
IIIA, 2.7	Bertrand, A.	1998	FINISH/EXP31039C, Determination of the freezing point Rhône-Poulenc Agro GLP or GEP: no Published: no	1998
IIIA, 2.7	Uceda, L. Le Gren, I.	1997	EXP31039C, Stability after 2 years storage at ambient temperature Rhône-Poulenc Agro Report/file N°: R&D/CRLD/AN/9715584 GLP or GEP: yes Published: no	1998

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Date of submission
IIIA, 2.5, 2.6	Uceda, L. Le Gren, I.	1997	EXP31039C, Determination of physico-chemical characteristics Rhône-Poulenc Agro Report/file N°: R&D/CRLD/AN/9716693 GLP or GEP: yes Published: no	1998

B.3 Data on application and further information

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Date of submission
IIA 3.5.1	M. K. Pedersen, J. D. Burton & H. D. Coble	1995	Effect of RPA90946 on auxin transport Proceedings of the 22nd Annual Meeting Plant Growth Regulation Society of America Hyatt Regency, Nicollet Mall Minneapolis, Minnesota July 18-20, 1995 GLP or GEP: no Published: yes	1998
IIA 3.5.1	M. K. Pedersen, J. D. Burton, J. Collins & H. D. Coble	1996	Activity of Cyclanilide as an Ethephon synergist Proceedings of the 23rd Annual Meeting Plant Growth Regulation Society of America University of Calgary Calgary, Alberta, Canada July 14-18, 1996 GLP or GEP: no Published: yes	1998
IIA 3.5.1	M. K. Pedersen, J.R. Collins, J. D. Burton, H. D. Coble & D. Fritz		Efficacy of Finish and its mechanism of action GLP or GEP: no Published: no	1998

B.4 Proposals for classification and labelling

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Date of submission
No studies have been submitted.				

B.5 Methods of analysis

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Date of submission
IIA, 4.1.2	Cousin, J. A.	1998	Validation data for the HPLC determination of RPA116741, Assessment GLP or GEP: no Published: no	1998
IIA, 4.2.1	Class, T.	1999	Determination of cyclanilide in cotton seed: Assessment (and consecutive validation) of Multi-Residue Enforcement Method(s) Rhône-Poulenc Agro Study 99-56 PTRL Europe Report No B 331 G GLP or GEP: yes Published: no	1999
IIA, 4.2.1	Cain, P.	1998	Cyclanilide, specificity of analytical methods for residues, Position paper GLP or GEP: no Published: no	1999
IIA, 4.2.3	Hausmann, S.	1999	Validation of the analytical method AR 113-95 for the determination of cyclanilide and its metabolite 2,4-dichloroaniline in surface water. Rhône Poulenc Agro Study No. 99-55 PTRL Europe Report No. B 329 G GLP or GEP: yes Published: no	1999
IIA, 4.2.1	Shaffer, S.R.	1995	Validation of methods for the analysis of cyclanilide (RPA090946) in Bovine Milk, Muscle, Kidney, Liver and Fat. Rhône-Poulenc Agro Horizon Laboratory Report/file N°: H #10123/ EC-95-294 GLP or GEP: yes Published: no	1999

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Date of submission
IIA, 4.2.1	Williams, M.	1994	Validation of methods for the analysis of RPA090946 in Cottonseed and cottonseed processed fractions Rhône-Poulenc Agro Horizon Laboratory Report/file N°: H #10079/ EC-94-272 GLP or GEP: yes Published: no	1999
IIA, 4.2.1	Williams, M	1995	Supplemental report for : Validation of methods for the analysis of RPA090946 in Cottonseed and cottonseed processed fractions Rhône-Poulenc Agro Horizon Laboratory Report/file N°: H #10079/ EC-94-272 GLP or GEP: yes Published: no	1999
IIA, 4.2.1	Williams, M	1995	Validation of methods for the analysis of RPA090946 in Cottonseed and cottonseed processed fractions, Supplemental report on method specificity Rhône-Poulenc Agro Horizon Laboratory Report/file N°: H #10079/ EC-94-272 GLP or GEP: yes Published: no	1999
IIIA, 5.1.1	Le Gren, I	1998	Ethephon, Determination by GLC analysis in formulation EXP31039C (SC) Rhône-Poulenc Agro Report N° : R&D/CRLD/AN/9815534 GLP or GEP: yes Published: no	1999

B.6 Toxicology and metabolism

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Date of submission
IIA, 5.4.2	Ham, A.L.	1998	Cyclanilide, *In Vivo/In Vitro* Unscheduled DNA Synthesis in Rat Primary Hepatocyte Cultures at Two Timepoints Rhône-Poulenc Agro Covance Report N° 18871-0-494 GLP or GEP: yes Published: no	1998
IIA, 5.2.6	Manciaux, X.	1999	Skin Sensitization Test in Guinea-Pigs (Maximization method of Magnusson, B. and Kligman, A.M.) Rhône-Poulenc Agro Covance Report N. 18053 TSG GLP or GEP: yes Published: no	1999

B.7 Residue data

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Date of submission
No new studies have been submitted.				

B.8 Environmental fate and behaviour

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Date of submission
IIA, 7.1.1	G. Reinken	2001	Kinetic modeling of the degradation in soil using bi-phasic kinetics Generated by: Aventis Submitted by: Aventis Report/file No: C011593 No GLP Not published	2001
IIIA, 9.1.3 IIIA, 9.2.1	G. Reinken	2001	Predicted Environmental Concentrations in soil and groundwater (PECsoil, PECGW) for the metabolite 2,4-DCA using bi-phasic kinetics Generated by: Aventis Submitted by: Aventis Report/file No: C011776 No GLP Not published	2001

B.9 Ecotoxicology

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Date of submission
IIA, 8.2.8	Hoberg, J.R	1995	RPA 090946, Toxicity to Duckweed, Lemna gibba, Rhône-Poulenc Agro Springborn Report N° 95-6-5922 GLP or GEP: yes Published: no	1999
IIA, 8.2.7	Odin-Feurtet, M.	1998	2,4-Dichloroaniline, Toxicity to the Sediment Dwelling Chironomid Larvae - 28 days (*Chironomus riparius*) Rhône-Poulenc Agro Report N° SA 98210 GLP or GEP: yes Published: no	1999
IIA, 8.7	C. Mead	1998	Cyclanilide assessment of the inhibitory effect on the respiration of activated sewage sludge. Rhône-Poulenc Agro SPL 282/531 GLP or GEP: yes Published: no	1999
IIA, 8.6	M. Berard	1999	Adjacent crops / results of screening data. Rhône-Poulenc Agro 06 November 1999 GLP or GEP: no Published: no	1999
IIIA, 10.5.2	Engelhard, E.K	1998	EXP31039C : An extended laboratory test to evaluate effects on *Aphidius rhopalosiphi* (Hymenoptera : Aphidiidae) Rhône-Poulenc Agro Springborn Report N° : 98-066-1013 GLP or GEP: yes Published: no	1999

SUMMARY REPORT
OF THE MEETING OF THE STANDING COMMITTEE ON PLANT HEALTH HELD ON 29 JUNE 2001 IN STOCKHOLM

President : G. Del Bino
All Member States were present.

1 **Examination and possible vote on a draft Commission Directive concerning the inclusion of Cyclanilide in Annex 1 to Council Directive 91/414/EEC** (Sanco/1285/2000 rev. 6; Review Report 7463/VI/98 rev. 4).

The Commission presented the Review Report on cyclanilide in document 7463/VI/98 rev. 4. The Committee took note of the Review Report.

The following declarations were made:

Commission: At the adoption of the Uniform Principles by Council in 1997, the Council and Commission agreed to the following declaration:

"The Council and the Commission note that application of this Directive is without prejudice to the legislation in force concerning the protection of workers. The Council and the Commission state that this principle will be unequivocally clarified in Directive 91/414/EEC on the occasion of the first amendment of that Directive. The Commission intends to submit a proposal for such amendment within one year from the date of notification of this Directive."

The Commission can for its part confirm its agreement with this declaration (subject to adequate adaptation of the deadline in the declaration).

The Commission presented the draft Diretive.

Vote : unanimous favourable opinion

The substance is a new active substance used as plant growth regulator.

The measures on which the Committee has given its opinion are subject to the appropriate procedures for formal adoption by the Commission.

A CHECCHI LANG
Director

EUROPEAN COMMISSION
HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL

Directorate C - Scientific Opinions
C3 - Management of scientific committees II; scientific co-operation and networks

SCIENTIFIC COMMITTEE ON PLANTS

SCP/CYCLAN/002-Final
14 December 2000

OPINION OF THE SCIENTIFIC COMMITTEE ON PLANTS ON THE EVALUATION OF CYCLANILIDE IN THE CONTEXT OF COUNCIL DIRECTIVE 91/414/EEC CONCERNING THE PLACING OF PLANT PROTECTION PRODUCTS ON THE MARKET

(Opinion adopted by the Scientific Committee on Plants on 30 November 2000)

Rue de la Loi 200, B-1049 Bruxelles/Wetstraat 200, B-1049 Brussel - Belgium - Office: B232 5/25.
Telephone: direct line (+32-2)295.77.05, switchboard 299.11.11. Fax: 295.73.32.

Internet: Michael.Walsh@cec.eu.int
D:\cd_dg24\brigitte\sources\dd_02_04_2001\SCP\2000\PPPs\Cycian2F,30.11.00_pdf.doc

1. TITLE

OPINION OF THE SCIENTIFIC COMMITTEE ON PLANTS ON THE EVALUATION OF CYCLANILIDE IN THE CONTEXT OF COUNCIL DIRECTIVE 91/414/EEC CONCERNING THE PLACING OF PLANT PROTECTION PRODUCTS ON THE MARKET
(Opinion adopted by the Scientific Committee on Plants on 30 November 2000)

2. TERMS OF REFERENCE

The Scientific Committee on Plants (SCP) is requested to respond to the following questions in the context of the Commission's work on the implementation of Council Directive 91/414/EEC concerning the placing of plant protection products on the market.

1) Does the SCP consider the effects on the mouse immune system to be of any relevance for man?

2) Does the SCP consider the teratological effects observed in the rabbit study to be of any relevance to man?

In addition, in the course of the evaluation of the documentation submitted to it, the Committee raised a specific environmental issue relating to the setting of the half-life for the soil metabolite 2,4-DCA.

3) The opinion of the Committee on this issue is expressed in Section 4.3.

3. BACKGROUND

The draft Commission Directive for inclusion of cyclanilide in Annex I to Directive 91/414/EEC concerning the placing of plant protection products on the market was submitted to the Committee for opinion. The Committee had been supplied with documentation comprising a draft evaluation report (monograph) prepared by the Rapporteur Member State (Greece) on the basis of a dossier prepared by the notifier (Rhône-Poulenc Agrochimie now Aventis CropScience), a review report prepared by the Commission and the Recommendations of the ECCO[1] Peer Review Programme.

Cyclanilide (RPA-90946) is a new active substance, intended for use in cotton field in combination with the plant growth regulator ethephon. The mixture of the two substances promotes boll opening, leaf abscission and inhibits growth following defoliation. The intended rate of use of cyclanilide ranges from 0.12 to 0.18kg a.s./ha.

[1] European Community Co-ordination.

4. OPINION

4.1 Question 1:

"Does the SCP consider the effects on the mouse immune system to be of any relevance for man?"

Opinion of the Committee:

The SCP does not consider the effects of cyclanilide on the thymus and spleen of mice relevant for the assessment of the risk in humans. Thymus involution and spleen depletion/atrophy were detected in mouse only at very high doses causing severe systemic effects and lethality. Thus, there is no sufficient evidence to conclude that the detected effects are related to a specific immunotoxic activity of cyclanilide. These effects should be considered to represent an unspecific response to stress following exposure to very high levels of the active substance. Further argument for the absence of specific immunotoxicity by cyclanilide is provided by the lack of any evidence of immunotoxicity in other short- and long-term toxicity studies.

Scientific background on which the opinion is based:

4.1.1 Toxicity profile

Cyclanilide is moderately toxic to rats, minimally irritant to the skin, and irritant to the eye. The toxicity profile from short-term and long-term studies in different species is characterised by macroscopic and microscopic pathology in liver, kidney, thymus, spleen, and mesenteric lymph nodes. Effects on reproduction are discussed in section 4.2. Behavioural neurotoxicity was reported in subchronic studies, with no evidence of neuropathological changes. An ADI[2] of 0.0075 mg/kg bw[3] was based on the NOAEL[4] of 1.5 mg/kg bw in the reproductive study in rats, and a safety factor of 200.

The concerns raised on the potential immunotoxicity of cyclanilide were based on the findings observed in the 90-day mouse study and also on studies in other species (1-year dog study and 2-year rat study).

4.1.2 Thymus involution and mortality in the 90-day mouse study

Groups of 10 mice/sex/dose were administered 0, 40, 200, 2000, and 4000 ppm of cyclanilide for 3 months. Mortality up to 50% occurred at the two highest doses (2000 and 4000 ppm), mainly during the first month. At 4000 ppm, decreased body weight and food consumption were observed at the beginning of the study. Macroscopic post-mortem examination did not reveal any specific cause of death. Toxic signs like lethargy, hypothermia, pallor and/or yellow staining of the anogenital area were observed in several animals prior to death.

Haematology and clinical chemistry findings were: decrease in platelet count at 2000 (not significant) and 4000 ppm (significant); significant elevation of serum AP activity at the

[2] Acceptable daily intake.
[3] Body weight.
[4] No observed adverse effect level.

two top doses; significant decrease in serum globulin and total protein levels in males at 4000 ppm. No effects were observed on total and differential WBC[5] counts.

The main microscopic findings in the animals which died were liver, lung and thyroid congestion, and gastric changes. Moderate to severe thymus involution and slight to severe spleen depletion/atrophy were observed. Malignant lymphoma of the lymphoreticular tissue was the cause of death in one female at 2000 ppm. There were no substance-related effects on other lymphoid organs. Mortality was attributed to acute stress. Animals surviving up to study termination did not show any alterations of thymus, spleen or other lymphoid organs.

The NOAEL was established at 200 ppm, equivalent to 34 mg/kg bw for males (37 mg/kg bw for females).

The observed changes in the thymus and spleen cannot be interpreted as primary "immunotoxic effects" because they were only observed in animals with severe or lethal systemic effects.

The observed changes in the thymus and spleen of animals which died during the first weeks of high-dose treatment may be interpreted as a response to acute stress occurring at the beginning of the study, when significant decreases in food consumption and body weight were observed. The evidence that stress can influence immunity and onset of diseases has been reported by several authors[6].

A single occurrence of lymphoreticular tissue malignant lymphoma cannot be related to the test substance administration. Even though its occurrence is not frequent in young animals, malignant lymphoma is the most common haematopoietic tumour in the CD-1 mice. Moreover, in the mice long-term study (18 months) neither an increase of lymphoreticular tissue tumours nor treatment-related effects on the lymphoid organs were seen.

4.1.3 Evidence from other studies

The short-term and long-term toxicity studies conducted with cyclanilide in different species were reviewed with the purpose of identifying possible effects on the immune system.

Chronic active inflammation in the liver was reported in the 1-year dog study, only in the top dose group (640 ppm), with central lobular hepatocellular degeneration and necrosis. This effect should be interpreted as a direct consequence of the extensive destruction of hepatic tissue, rather than as an immune effect.

Lung purulent inflammation/abscesses and sub-acute and chronic inflammation and fibrosis of the visceral pleura/capsule were reported in the 2-year rat study, at the end of study, but not at interim sacrifice. These findings were restricted to the high dose animals (1000 ppm). No effects on lymphoid organs were observed. This effect should be considered as a response to acute stress due to the high doses administered to aged rats.

[5] White blood cell.
[6] See ref. 2 Dean *et al.*

Markers of possible effects on the immune system (total and differential leukocyte counts, serum globulin levels, weight changes and histology of lymphoid organs) were not affected in any of the short- and long-term studies.

4.1.4 Conclusions

Since thymus involution and spleen depletion/atrophy were detected in the mouse only at very high doses causing severe systemic effects and lethality, there is no sufficient evidence to conclude that these effects are related to a specific immunotoxic activity of cyclanilide; these effects should be considered to represent an unspecific response to stress following exposure to high levels of cyclanilide.

Further argument for the absence of specific immunotoxicity by cyclanilide is provided by the observation that no consistent evidence of immunotoxicity of cyclanilide was observed in any of the other short- and long-term toxicity studies.

4.2 Question 2

Does the SCP consider the teratological effects observed in the rabbit study to be of any relevance to human?

Opinion of the Committee:

The SCP does not consider the results of the rabbit study indicative of reproductive toxicity potential of cyclanilide to humans. The reported findings in the rabbit study are considered substance related, however they were only observed in the top-dose animals showing salient signs of systemic toxic effects. The types of effects on reproduction were all seen also in control rabbits either in the present study or in control groups from previous studies in the performing laboratory (historical controls). In addition no similar effects of cyclanilide on reproduction were seen in other studies for reproductive toxicity i.e. teratology study in rats or two generation reproductive toxicity study in rats.

Scientific background on which the opinion is based:

4.2.1 Toxicological evaluation

No specific effects of cyclanilide on reproduction were seen in studies for reproductive toxicity in rats, i.e. teratology study and two generation reproductive toxicity study.

The Rapporteur Member State has established an ADI of 0.0075 mg for the active substance using the NOAEL of 1.5 mg/kg bw/ day in the reproductive toxicity study in rats based upon renal lesions (microscopic mineralization foci in the renal papilla and microscopic calculi in the renal pelvis) observed in the F_1 females and applying an uncertainty factor of 200 (the additional safety factor of 2 is applied as NOAEL is considered as a LOEL[7]).

[7] Lowest observable effect level.

4.2.2 The teratology study in rabbits[8]

The teratology study in rabbits is a well reported study performed in compliance with GLP. Cyclanilide was administered to pregnant rabbits (artificial insemination) during the period of major organogenesis, gestation day 6 through gestation day 18. The 20 females per group received 0 (controls), 3, 10 and 30 mg/kg bw/ day in 0.5 ml corn oil.

The animals dosed 30 mg/kg bw/day showed overt signs of toxicity including wobbly gait, partial hind limb paralysis, decreased activity and partial hair loss. In addition body weight gain and food consumption were markedly reduced during the treatment period.

Two females in the top dose group and one in the control group aborted on gestation days 18, 20 and 28 respectively. No remarkable internal findings were observed at necropsy. A slight but not statistically significant increase was noted in the number of early resorptions at the 30 mg/kg bw/day level when compared to the control group. This finding was due to a slightly lower than normal group value in the controls and two females with total litter resorption. A correspondent slight increase in mean post implantation loss was recorded. Embryo-foetal death is known to be a consequence of salient toxicity in dam as observed in the present study[9]. Death of an embryo or foetus is usually followed by resorption of the tissue or abortion in rabbits[10].

No statistically significant increase in the incidence of treatment-induced malformations nor foetal weight effects were noted. Some scattered foetal findings were observed, some of which only occurred in the dosed animals. The type of effects (e.g. heart and/or great vessel anomaly, right-sided retro-oesophageal aortic arch, extra site of ossification anterior to sternebra 1, 8th sternal costal cartilage, 25 presacral vertebrae, 7th sternebrae, and reduced ossification of the skull) have however all been seen in control animals either in the present study or in control groups from previous studies in the performing laboratory (historical controls). The incidence of the individual findings was close to or within the range of the historical controls of this rabbit strain. It is a common observation that treatment at very high maternally toxic dose levels can provoke small increase (2-3 fold) in the number of foetus with abnormalities[11].

4.2.3 Conclusion

The SCP considers the findings in the study substance related and as such relevant for human risk assessment. However, the SCP does not consider the data indicative of a reproductive toxicity potential of cyclanilide to humans for the following reasons:

- The effect of cyclanilide on reproduction is only observed in the top-dose animals showing salient signs of systemic toxicity.

- The types of effects on reproduction are all seen in control animals either in the present study or in control groups from previous studies in the performing laboratory (historical controls).

[8] See Rodwell, D.E. Teratology study in rabbits with RPA 090946, January 3, 1991.
[9] See Barlow and Sullivan, 1982, Khera, 1985
[10] See Barlow and Sullivan 1982.
[11] See Barlow and Sullivan 1982.

- The slight but not statistically significant increase in embryolethality noted in the high dose group, can be considered to be a consequence of salient toxicity in dams.

- No similar effects of cyclanilide on reproduction were seen in other studies for reproductive toxicity i.e. teratology study in rats or two generation reproductive toxicity study in rats.

4.3 Specific issue raised by the SCP

The Committee has noticed that the DT_{50} value of 2.5 days (as calculated by "Model Manager" version 1.1[12]) for the soil metabolite 2,4-dichloroaniline (as reported in Appendix II: Endpoints and related information) is not consistent with the experimental results as summarised by the Rapporteur Member State: "2,4-DCA increased from 3% at day 1 to 10% at 14 days and decreased to 5% at the end of the study (180 days)". Therefore the Committee recommends that the estimation procedure for this half-life is re-evaluated.

Opinion of the Committee:

The Committee recommends that the estimation procedure for the half-life for the soil metabolite 2,4-dichloroaniline is re-evaluated.

5. REFERENCES

1. EHC 180. Environmental Health Criteria. Principles and methods for assessing direct immunotoxicity associated with exposure to chemicals. IPCS/WHO, 1996.

2. Dean, J.H., Cornacoff, J.B., Rosenthal G.J., AND Luster, M.I. (1994). Immune system. Evaluation of injury. In: *"Principles and methods of toxicology"*- A. Wallace Hayes Ed., 3rd edition. Raven Press, New York, pp. 1065-1090.

3. van Loveren, H., and Vos, J.C. (1992). Evaluation of OECD Guideline No 407 for assessment of toxicity of chemicals with respect to potential adverse effects to the immune system (RIVM report no. 158801001). National Institute of Public Health and Environmental Protection, Bilthoven, The Netherlands.

4. Luster, M.I., Portier, C., Pait, D.G., White, K.G.L. Jr, Gennings, C., Munson, A.E., Rosenthal, G.J. (1992). Risk Assessment in Immunotoxicology. I. Sensitivity and Predictability of Immune Tests. *Fund. Appl. Toxicol.*, **18**: 200-210.

5. Luster, M.I., Munson, A.E., Thomas, P.T., Holsapple, M.P., Fenters, J.D., White, K.L., Lauer, L.D., Germolec, D.R., Rosenthal, G.J., and Dean, J.H. (1988). Development of a testing battery to assess chemical-induced immunotoxicity: National Toxicology Program's Guidelines for immunotoxicity evaluation in mice. *Fundam. Appl. Toxicol.*, **10**: 2-19.

6. Van Loveren, H., and Vos J.G. (1989). Immunotoxicological considerations: a practical approach to immunotoxicity testing in the rat. In: *"Advances in applied*

[12] Modelling software package from Cherwell Scientific Ltd, Oxford, UK.

toxicology", Dayan A.D., and Paine, A.J. Edrs. London, Taylor & Francis, pp. 143-165.

7. Rodwell, D.E. Teratology study in rabbits with RPA 090946. Springborn Laboratories, INC. Submitted by Rhône-Poulenc Agrochimie. Report/ file N°: SLS 3147.73 Date: January 3, 1991.

8. Rodwell, D.E. Teratology study in rats with RPA 090946. Springborn Laboratories, INC. Submitted by Rhône-Poulenc Agrochimie. Report/ file N°: SLS 3147.71 Date: December 12, 1990.

9. Tyl, R.W., Myers, C.B., Marr, M.C. Two generations reproductive study of RPA 090946 administered in the feed to CD (Sprague – Dawley) rats. Centre for Life Sciences and Toxicology. Submitted by: Rhône-Poulenc Agrochimie. Report/ file N°: RTI 65C-5250 Date: December 7, 1994.

10. Khera, K.S. Maternal Toxicity: A possible etiological factor in embryo-foetal deaths and foetal malformations of rodents-rabbit species. Teratology 31, 129-153, 1985.

11. Barlow, Susan M. and Frank M. Sullivan. Reproductive toxicity testing in animals in reproductive hazards of industrial chemicals. Academic Press, 1982.

12. Debruyne E. and Semino G. Cyclanilide, response document to the ECCO 73 Peer review meeting: request of mechanistic study on the immune system. Rhône-Poulenc Toxicology Department, March 1999.

6. DOCUMENTATION MADE AVAILABLE TO THE COMMITTEE

1. Evaluation of cyclanilide in the context of Council Directive 91/414/EEC concerning the placing of plant protection products on the market (Doc. SCP/CYCLAN/001), submitted by DG SANCO, 3 April 2000.

2. Cyclanilide: Evaluation table 7462/VI/98rev. 9 (Doc. SCP/CYCLAN/003-Rev.1), submitted by DG SANCO, 31 May 2000.

3. Cyclanilide: Review report for the active substance 7463/VI/98-rev. 1 (Doc. SCP/CYCLAN/004), submitted by DG SANCO, 31 May 2000.

4. Evaluation of cyclanilide in the context of Council Directive 91/414/EEC concerning the placing of plant protection products on the market: Appendices (Doc. SCP/CYCLAN/005-Rev. 1), submitted by DG SANCO, 13 June 2000.

5. Reconsideration of effect on reproduction of the current LOEL, safety factor and derived ADI and AOEL (Doc. SCP/CYCLAN/009), submitted by DG SANCO, 5 June 2000.

6. Cyclanilide: Volume 3 Annex B ADDENDUM to the draft Assessment Report prepared by Greece, June 2000 (Doc. SCP/CYCLAN/020), submitted by DG SANCO, 15 June 2000.

7. Attachment to the monograph of cyclanilide: volume 3, Annex B 7: Environmental fate and behaviour – March 2000 (Doc. SCP/CYCLAN/021), submitted by DG SANCO, 15 June 2000.

8. Cyclanilide: Evaluation of additional data by the RMS, Section: Fate and behaviour in the environment – 14 March 2000 (Doc. SCP/CYCLAN/022), submitted by DG SANCO 15 June 2000.

9. Letter from Greek authority (Doc. SCP/CYCLAN/023), submitted by DG SANCO, 15 June 2000.

10. Danish comments on the full report and the evaluation table (Doc. SCP/CYCLAN/006), submitted by DG SANCO, 15 June 2000.

11. Comment from Denmark to RMS concerning aquatic ecotoxicology (Doc. SCP/CYCLAN/007), submitted by DG SANCO, 15 June 2000.

12. Response from Greece on Danish comments (Doc. SCP/CYCLAN/008), submitted by DG SANCO, 5 June 2000.

13. Comments from Austria relating to Lemna study with the formulation (Doc. SCP/CYCLAN/010), submitted by DG SANCO, 15 June 2000.

14. Comments from Austria relating to Lemna study (Doc. SCP/CYCLAN/011).

15. Comments from Greece (Doc. SCP/CYCLAN/012), submitted by DG SANCO, 15 June 2000.

16 Comments from The Netherlands (Doc. SCP/CYCLAN/013), submitted by DG SANCO, 15 June 2000.

17. Comments from the United Kingdom (Doc. SCP/CYCLAN/014), submitted by DG SANCO, 15 June 2000.

18. Comments from France (Doc. SCP/CYCLAN/015), submitted by DG SANCO, 15 June 2000.

19 Response from RMS to Austrian comments on the need for a Lemna study with the formulation (Doc. SCP/CYCLAN/016), submitted by DG SANCO, 15 June 2000.

20. Response from RMS to Danish comments on the need for a Lemna study with the formulation (Doc. SCP/CYCLAN/017), submitted by DG SANCO, 15 June 2000.

21. Response from RMS to comments from Belgium on the evaluation table 74/VI/98 rev.3 (Doc. SCP/CYCLAN/018), submitted by DG SANCO, 15 June 2000.

22. Response from RMS to comments from France on the evaluation table 74/VI/98 rev.6 (Doc. SCP/CYCLAN/019), submitted by DG SANCO, 15 June 2000.

23. Danish comments to the list of end points (Doc. SCP/CYCLAN/024), submitted by DG SANCO, 25 May 2000..

24. Draft evaluation report (Monograph) prepared in the context of inclusion of cyclanilide in Annex I of Council Directive 91/414/EEC – Ministry of Agriculture, Greece (Volumes 1 to 4 – January 1998).

25 Cyclanilide/evaluation of additional data. S. Vizantinopolous (2000). Letter from NAGREF to Ministry of Agriculture of Greece, 14 March 2000.

7. ACKNOWLEDGEMENTS

The Committee wishes to acknowledge the contributions of the working groups that prepared the initial draft opinion:

Toxicology WG: Prof. Maroni (Chairman) and Committee members: Dr. Delcour-Firquet, Dr. Meyer, Dr. Moretto, Prof. Savolainen, Prof. Silva Fernandes, Dr. Speijers and invited expert Dr. Fait.

Environmental assessment WG: Prof. Hardy (Chairman) and Committee members: Mr. Koepp, Dr. Sherratt, Prof. Silva Fernandes, invited experts: Dr. Boesten, Dr. Carter, Dr. Forbes and Dr. Luttik.

Berichte aus der Biologischen Bundesanstalt für Land- und Forstwirtschaft erscheinen seit 1995 in zwangloser Folge.

Heft 89, 2001: EU-Beurteilungsbericht Zineb. Rechtliche Regelungen der Europäischen Union zu Pflanzenschutzmitteln und deren Wirkstoffen. Band D 23.
Bearbeitet von Herbert Köpp und Elke Leske, getr. Zählung.

Heft 90, 2001: EU-Beurteilungsbericht Thiabendazol. Rechtliche Regelungen der Europäischen Union zu Pflanzenschutzmitteln und deren Wirkstoffen. Band D 24.
Bearbeitet von Herbert Köpp und Elke Leske, getr. Zählung.

Heft 91, 2001: EU-Beurteilungsbericht Fenhexamid. Rechtliche Regelungen der Europäischen Union zu Pflanzenschutzmitteln und deren Wirkstoffen. Band D 24.
Bearbeitet von Herbert Köpp und Elke Leske, getr. Zählung.

Heft 92, 2001: Liste der zugelassenen Pflanzenschutzmittel (Stand: 1. Juli 2001).
Bearbeitet von Dr. Achim Holzmann, 88 S.

Heft 93, 2001: Pflanzenschutz im ökologischen Landbau.
PD Dr. habil. Stefan Kühne, Dr. Marga Jahn, Dr. Mario Wick und Dr. Holger Beer, 52 S.

Heft 94, 2002: EU-Beurteilungsbericht Glyphosat. Rechtliche Regelungen der Europäischen Union zu Pflanzenschutzmitteln und deren Wirkstoffen. Band D 26.
Bearbeitet von Dr. Henning Bruno und Susanne Schaper, getr. Zählung.

Heft 95, 2002: Pflanzenschutz im ökologischen Landbau – Probleme und Lösungsansätze.
Fünftes Fachgespräch am 28. Juli 2001 in Kleinmachnow. Hinreichende Wirksamkeit von Pflanzenschutzmitteln im ökologischen Landbau. Saat- und Pflanzgut für den ökologischen Landbau.
Bearbeitet von PD Dr. habil. Stefan Kühne und Britta Friedrich, 177 S.

Heft 96, 2002: Liste der zugelassenen Pflanzenschutzmittel (Stand: 1. Januar 2002).
Bearbeitet von Andreas Spinti, 74 S.

Heft 97, 2002: EU-Beurteilungsbericht 2,4-D. Rechtliche Regelungen der Europäischen Union zu Pflanzenschutzmitteln und deren Wirkstoffen. Band D 27.
Bearbeitet von Dr. Martina Erdtmann-Vourliotis und Susanne Schaper, getr. Zählung.

Heft 98, 2002: NEPTUN 2000 – Erhebung von Daten zum tatsächlichen Einsatz chemischer Pflanzenschutzmittel im Ackerbau Deutschlands. Dr. Dietmar Roßberg, Dr. Volkmar Gutsche, Dr. Siegfried Enzian und Dr. Mario Wick, 27 S., Anhang.

Heft 99, 2002: EU-Beurteilungsbericht Thifensulfuron-methyl. Rechtliche Regelungen der Europäischen Union zu Pflanzenschutzmitteln und deren Wirkstoffen. Band D 28.
Bearbeitet von Dr. Martina Erdtmann-Vourliotis und Susanne Schaper, getr. Zählung.

Heft 100, 2002: EU-Beurteilungsbericht Flupyrsulfuron-methyl. Rechtliche Regelungen der Europäischen Union zu Pflanzenschutzmitteln und deren Wirkstoffen. Band D 29.
Bearbeitet von Dr. Henning Bruno und Susanne Schaper, getr. Zählung.

Heft 101, 2002: EU-Beurteilungsbericht *Paecilomyces fumosoroseus*. Rechtliche Regelungen der Europäischen Union zu Pflanzenschutzmitteln und deren Wirkstoffen. Band D 30.
Bearbeitet von Dr. Martina Erdtmann-Vourliotis, Dr. Axel Wilkening und Susanne Schaper, getr. Zählung.

Heft 102, 2002: EU-Beurteilungsbericht Isoproturon. Rechtliche Regelungen der Europäischen Union zu Pflanzenschutzmitteln und deren Wirkstoffen. Band D 31.
Bearbeitet von Dr. Henning Bruno und Susanne Schaper, getr. Zählung.

Heft 103, 2002: Zuständigkeiten bei der Prüfung und Zulassung von Pflanzenschutzmitteln und bei der EU-Wirkstoffprüfung.
Stand: Februar 2002. Bearbeitet von Edelgard Adam, 58 S.

Heft 104, 2002: Pflanzenschutz im ökologischen Landbau – Probleme und Lösungsansätze.
Sechstes Fachgespräch am 26. Juni 2001 in Braunschweig. Abwehr von Wühlmausschäden im ökologischen Landbau. Bearbeitet von Dr. Hans-Joachim Pelz, 109 S.

Heft 105, 2002: EU-Beurteilungsbericht Acibenzolar-S-methyl. Rechtliche Regelungen der Europäischen Union zu Pflanzenschutzmitteln und deren Wirkstoffen. Band D 32.
Bearbeitet von Herbert Köpp und Susanne Schaper, getr. Zählung.

Heft 106, 2002: EU-Beurteilungsbericht Eisen(III)phosphat. Rechtliche Regelungen der Europäischen Union zu Pflanzenschutzmitteln und deren Wirkstoffen. Band D 33.
Bearbeitet von Dr. Martina Erdtmann-Vourliotis, Dr. Axel Wilkening und Susanne Schaper, getr. Zählung.

Heft 107, 2002: EU-Beurteilungsbericht Ethofumesat. Rechtliche Regelungen der Europäischen Union zu Pflanzenschutzmitteln und deren Wirkstoffen. Band D 34.
Bearbeitet von Dr. Martina Erdtmann-Vourliotis und Susanne Schaper, getr. Zählung.