

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO	
RAD: 14-121257- -2	FECHA: 2015-05-16 23:27:08
DEP: 2020 DIRECCION DE NUEVAS CREACIONES	EVE: 378 FASE NACIONAL INCLUIDO CAPITULO I
TRA: 11 PCT-PATENTE DE INVENCION CAPITULOS I Y II	FOLIOS: 62
ACT: 430 REQUERSOLICITA	

DIRECCIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado(a)/Señor(a)
HELENA CAMARGO WILLIAMSON

Asunto: Radicación: 14-121257- -2
 Trámite: 11
 Evento: 378
 Actuación: 430
 Oficio: 5339
 Folios: 62

Patente de Invención	X			Patente de Modelo de Utilidad	
Vía Nacional					
Vía PCT (Fase Nacional)	X	Capítulo I	X	Capítulo II	
No. Solicitud Internacional	PCT/EP2012/075255				
Fecha de Presentación Internacional	12/12/2012				

Como resultado del examen de fondo realizado, con fundamento en el Artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se comunica:

1. Documentos estudiados

Descripción:	Radicado 14-121257-00000-0000	05/Junio//2014
Reivindicaciones:	Radicado 14-121257-00000-0000	05/Junio//2014
Prioridad:	EP 11193829.6	15/Diciembre/2011

2. Análisis de la Prioridad

Se acepta la reivindicación de prioridad porque ésta solicitud fue presentada dentro del plazo establecido (Art. 9 D 486) y su contenido técnico corresponde con el de la prioridad reivindicada.

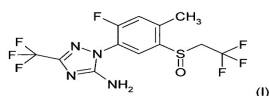
3. Objeto de la invención

De acuerdo con lo establecido en el numeral 1.2.2.2 del Capítulo Primero del Título X de la Circular Única para efectos del examen de patentabilidad, se tendrá en cuenta la tasa pagada por el solicitante al momento de comenzar el examen para las reivindicaciones adicionales; esto es que cuando la solicitud contenga más de diez (10) reivindicaciones y no se haya pagado la tasa complementaria, sólo se estudiarán las cubiertas por la tasa pagada. Con relación a la presente solicitud se realizó el pago de las reivindicaciones adicionales y se estudiarán las reivindicaciones 1 a 13 de acuerdo con el radicado 14-121257-00000-0000.

Título de la solicitud: "Combinaciones de principios activos que tienen propiedades insecticidas y acaricidas".

El problema planteado en esta solicitud consiste en la necesidad de suministrar combinaciones que comprendan ingredientes activos útiles para combatir insectos y ácaros en plantas.

Para resolver este problema técnico la solicitud en estudio proporciona una combinación del compuesto de fórmula (I) con un insecticida y/o acaricida.



El objeto de la presente solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): A01P 7/00; A01N 43/653, 63/00, 63/04, 43/90, 47/40, 53/00, 43/88, 43/56, 43/36, 57/16, 51/00, 47/34, 57/12 y 47/02.

4. Reivindicaciones relativas a un uso (Art 14 D 486).

El uso de las reivindicaciones 7-12 no es patentable, de acuerdo con el Art 14. Aunque la reivindicación 12 se encabece como un método para reducir el daño general de plantas y partes de plantas, reclama la aplicación de la combinación sobre la planta lo que hace referencia al uso y de acuerdo al artículo citado el mismo no es patentable.

5. De la solicitud de patente

Título

El título no permite identificar el alcance de la invención ya que define de forma general las combinaciones en términos de su actividad biológica, por lo anterior, se sugiere restringir el título incluyendo las características técnicas inventivas.

Reivindicaciones (Art 30 D 486, Art 22 PCT)

La reivindicación 1 se encabeza como una combinación entre los compuestos de fórmula I y un segundo agente activo, sin embargo, de acuerdo con los ejemplos sustentados lo definido corresponde a composiciones, por lo que, se sugiere

cambiar el encabezado combinación por composición; se recuerda que, las combinaciones pueden hacer referencia a un método de tratamiento, el cual no es objeto de patentabilidad. Por lo anterior, las reivindicaciones deben ser claras en cuanto al tipo producto que reclaman.

La reivindicación 1 no es clara porque hace referencia a la descripción, según las expresiones “(conocida por el documento WO2005/077934)”, “(conocida por el documento WO2007/115644)”, “(conocida por el documento WO2007/115643)”, “(conocida por el documento EP-A-0539588)”, “(conocida por el documento WO2007/149134)”, “(conocida por el documento WO2007/074751)”, “(conocida por el documento WO2006/089633)”, “(conocida por el documento WO2008/067911)”, “(conocida por el documento WO2006/043635)”, “(conocida por el documento WO2006/100288)”, “(conocida por el documento WO2007/057407)”, “(conocida por el documento WO2003/106457)”, “(conocida por el documento WO2009/049851)”, “(conocida por el documento WO2009/099160)”, “(conocida por el documento WO2005/063094)”, “(conocida por el documento JP2010/018586)”, “(conocida por el documento WO2007/075459)”, “(conocida por el documento WO2005/085216)”, “(conocida por el documento WO2010/005692)”, “(conocida por el documento WO2002/096882)”, “(conocida por el documento WO2005/085216)”, “(conocida por el documento WO2007/101369)”, “(conocida por el documento WO2010/006713)”, “(conocida por el documento WO2010/069501)”, “(conocida por el documento CN 102057925)”, “(conocida por el documento WO2011/049233)”, “(conocida por el documento WO2008/066153)”, “(conocida por el documento WO2010/043122)”, “(conocida por el documento WO2010/139271)”, “(conocida por el documento WO2007/000098)” y “(conocida por el documento WO2012/034472)”. Se sugiere eliminar la referencia a la descripción.

La reivindicación 1 no es clara porque las expresiones “uno o más” o “por ejemplo” precediendo una característica no es limitativa, porque hace opcional a la característica y no precisa el alcance de la reivindicación. Se sugiere incluir una expresión concreta de acuerdo con los ejemplos sustentados.

La reivindicación 1 no es clara porque define los ingredientes activos en términos de su acción biológica o de su mecanismo de acción, se recuerda, que los ingredientes activos se nombran a través de su denominación común internacional o nombre químico IUPAC y en el caso de los agentes biológicos a través de su nombre científico, se sugiere hacer las aclaraciones necesarias.

Las Reivindicaciones 1 y 4-6 incluyen la expresión “insecticidas y/o acaricidas y/o agente de combate biológico” que refiere el uso de la combinación reivindicada, el cual no es una característica técnica que defina a la invención. Se sugiere eliminar dichas expresiones.

Las reivindicaciones 1, 4-7 y 13 no son concisas porque las definiciones de insecticidas, acaricidas y agentes de combate biológico son generales, se sugiere restringir la solicitud a una razonable generalización de los insecticidas, acaricidas y agentes de combate biológico, es decir, que se encuentren debidamente

sustentados a través de ejemplos concretos de acuerdo con lo presentado en la tabla No. 1.

Tabla No 1. Ingredientes activos/Excipientes de las composiciones soportadas.

Ingrediente activo/Excipiente	Ejemplos sustentados
Disolvente:	Acetona y dimetilformamida
Emulsionantes	No define (alquilarylpoliglicoléter)
Tensioactivos	No sustenta
Diluyentes	No sustenta
Combinaciones	Compuesto de fórmula (I) + Acrinatrina Compuesto de fórmula (I) + Imidacloprid Compuesto de fórmula (I) + Clotianidina Compuesto de fórmula (I) + Dinotefuran Compuesto de fórmula (I) + Clorpirifos Compuesto de fórmula (I) + Sulfoxaflor Compuesto de fórmula (I) + Flupiradifurona Compuesto de fórmula (I) + Azadiractina Compuesto de fórmula (I) + <i>Bacillus subtilis</i> cepa GB 03 Compuesto de fórmula (I) + <i>Bacillus subtilis</i> Compuesto de fórmula (I) + Granolovirus de Cydia pomonella Compuesto de fórmula (I) + Clorantraniliprol Compuesto de fórmula (I) + Milbemectina Compuesto de fórmula (I) + Pimetrozina Compuesto de fórmula (I) + Lambda-cihalotrina Compuesto de fórmula (I) + Dimetoato Compuesto de fórmula (I) + Flupiradifurona Compuesto de fórmula (I) + Fipronilo Compuesto de fórmula (I) + benzoato de emamectina Compuesto de fórmula (I) + Lepimectina Compuesto de fórmula (I) + Tiametoxan Compuesto de fórmula (I) + Clorantraniliprol Compuesto de fórmula (I) + Alfa-cipermetrina Compuesto de fórmula (I) + Bifentrina Compuesto de fórmula (I) + Tiacloprid Compuesto de fórmula (I) + acetamiprid Compuesto de fórmula (I) + Nitenpiram Compuesto de fórmula (I) + Teflutrina Compuesto de fórmula (I) + Flufenoxuron Compuesto de fórmula (I) + triflumuron Compuesto de fórmula (I) + Beta-ciflutrina Compuesto de fórmula (I) + Tiodicarb Compuesto de fórmula (I) + Diflubenzuron Compuesto de fórmula (I) + Bifetrina Compuesto de fórmula (I) + Cipermetrina Compuesto de fórmula (I) + Deltametrina Compuesto de fórmula (I) + Beta-ciflutrina Compuesto de fórmula (I) + Indoxacarb Compuesto de fórmula (I) + Fluensulfona Compuesto de fórmula (I) + protein harpin Compuesto de fórmula (I) + <i>Metschnikowia fructicola</i> Compuesto de fórmula (I) + <i>Paecilomyces lilacinus</i> cepa 251 Compuesto de fórmula (I) + piretrum Compuesto de fórmula (I) + Bupofezina Compuesto de fórmula (I) + Pirifluquinazona Compuesto de fórmula (I) + Espinetoram Compuesto de fórmula (I) + Espinosad Compuesto de fórmula (I) + Clorfenapir Compuesto de fórmula (I) + Tebufenpirad

	Compuesto de fórmula (I) + Abamectina Compuesto de fórmula (I) + <i>Bacillus firmus</i> I-1582 Compuesto de fórmula (I) + Timol Compuesto de fórmula (I) + <i>Metarhizium anisopliae</i> cepa F52 Compuesto de fórmula (I) + <i>Bacillus pumilus</i> cepa QST2808 Compuesto de fórmula (I) + <i>Bacillus thuringiensis</i> spp aizawai Compuesto de fórmula (I) + <i>Bacillus amyloliquefaciens</i> FZB42 Compuesto de fórmula (I) + <i>Bacillus subtilis</i> QST712 Compuesto de fórmula (I) + 1-(3-cloropiridin-2-il)-N-[4-ciano-2-metil-6-(metilcarbamoil)fenil]-3-[[5-(trifluorometil)-1H-tetrazol-1-il]metil]-1H-pirazol-5-carboxamida.
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Se sugiere eliminar las características no sustentadas del capítulo reivindicatorio.

La reivindicación 13 menciona que la combinación de activos comprende diluyentes y/o tensioactivos lo que refiere una composición, se recuerda que las composiciones se deben definir en términos de sus ingredientes y proporciones, en donde, los ingredientes activos se nombran a través de su denominación común internacional o nombre químico IUPAC y los excipientes en términos de su nombre común, se sugiere hacer las precisiones pertinentes.

Debido a que la solicitud se refiere a material biológico, es necesario presentar el Certificado de Depósito para las cepas: *Bacillus subtilis* QST712, *Bacillus amyloliquefaciens* FZB42, *Bacillus pumilus* cepa QST2808, *Metarhizium anisopliae* cepa F52, *Paecilomyces lilacinus* cepa 251 y *Bacillus subtilis* cepa GB 03.

Se requiere al solicitante hacer las aclaraciones necesarias.

6. Unidad de invención (Art 25 D 486)

La solicitud no cumple con el requisito de unidad de invención porque se refiere a 58 grupos inventivos. El concepto común de la presente solicitud es una combinación de ingredientes activos que consiste en el compuesto de fórmula (I) y un compuesto insecticida o acaricida, para el control de insectos y ácaros en plantas, sin embargo, este concepto común no es nuevo ya que el documento US20090076282, describe combinaciones seguras con alto efecto pesticidas y bajo efecto residual conformadas por compuestos derivados de 3-triazolil-fenil-sulfido con compuestos con actividad insecticida, acaricida y nematocida, útiles en la prevención y/o tratamiento de la infestación por parte de insectos, ácaros y nematodos en plantas de granja o de jardín. Por lo tanto, los grupos inventivos están definidos por las siguientes características esenciales:

1. Compuesto de fórmula (I) + Acrinatrina. Reivindicaciones 1-6.
2. Compuesto de fórmula (I) + Imidacloprid. Reivindicaciones 1-6.
3. Compuesto de fórmula (I) + Clotianidina. Reivindicaciones 1-6.
4. Compuesto de fórmula (I) + Dinotefuran. Reivindicaciones 1-6.
5. Compuesto de fórmula (I) + Clorpirifos. Reivindicaciones 1-6.
6. Compuesto de fórmula (I) + Sulfoxaflor. Reivindicaciones 1-6.
7. Compuesto de fórmula (I) + Flupiradifurona. Reivindicaciones 1-6.
8. Compuesto de fórmula (I) + Azadiractina. Reivindicaciones 1-6.
9. Compuesto de fórmula (I) + *Bacillus subtilis* cepa GB 03. Reivindicaciones 1-6.
10. Compuesto de fórmula (I) + *Bacillus subtilis*. Reivindicaciones 1-6.

11. Compuesto de fórmula (I) + Granolovirus de Cydia pomonella. Reivindicaciones 1-6.
12. Compuesto de fórmula (I) + Clorantraniliprol. Reivindicaciones 1-6.
13. Compuesto de fórmula (I) + Milbemectina. Reivindicaciones 1-6.
14. Compuesto de fórmula (I) + Pimetrozina. Reivindicaciones 1-6.
15. Compuesto de fórmula (I) + Lambda-cihalotrina. Reivindicaciones 1-6.
16. Compuesto de fórmula (I) + Dimetoato. Reivindicaciones 1-6.
17. Compuesto de fórmula (I) + Flupiradifurona. Reivindicaciones 1-6.
18. Compuesto de fórmula (I) + Fipronilo. Reivindicaciones 1-6.
19. Compuesto de fórmula (I) + benzoato de emamectina. Reivindicaciones 1-6.
20. Compuesto de fórmula (I) + Lepimectina. Reivindicaciones 1-6.
21. Compuesto de fórmula (I) + Tiametoxan. Reivindicaciones 1-6.
22. Compuesto de fórmula (I) + Clorantraniliprol. Reivindicaciones 1-6.
23. Compuesto de fórmula (I) + Alfa-cipermetrina. Reivindicaciones 1-6.
24. Compuesto de fórmula (I) + Bifentrina. Reivindicaciones 1-6.
25. Compuesto de fórmula (I) + Tiaclopid. Reivindicaciones 1-6.
26. Compuesto de fórmula (I) + acetamiprid. Reivindicaciones 1-6.
27. Compuesto de fórmula (I) + Nitenpiram. Reivindicaciones 1-6.
28. Compuesto de fórmula (I) + Teflutrina. Reivindicaciones 1-6.
29. Compuesto de fórmula (I) + Flufenoxuron. Reivindicaciones 1-6.
30. Compuesto de fórmula (I) + Triflumuron. Reivindicaciones 1-6.
31. Compuesto de fórmula (I) + Beta-ciflutrina. Reivindicaciones 1-6.
32. Compuesto de fórmula (I) + Tiodicarb. Reivindicaciones 1-6.
33. Compuesto de fórmula (I) + Diflubenzuron. Reivindicaciones 1-6.
34. Compuesto de fórmula (I) + Bifetrina. Reivindicaciones 1-6.
35. Compuesto de fórmula (I) + Cipermetrina. Reivindicaciones 1-6.
36. Compuesto de fórmula (I) + Deltametrina. Reivindicaciones 1-6.
37. Compuesto de fórmula (I) + Beta-ciflutrina. Reivindicaciones 1-6.
38. Compuesto de fórmula (I) + Indoxacarb. Reivindicaciones 1-6.
39. Compuesto de fórmula (I) + Fluensulfona. Reivindicaciones 1-6.
40. Compuesto de fórmula (I) + Protein harpin. Reivindicaciones 1-6.
41. Compuesto de fórmula (I) + *Metschnikowia fructicola*. Reivindicaciones 1-6.
42. Compuesto de fórmula (I) + *Paecilomyces lilacinus* cepa 251. Reivindicaciones 1-6.
43. Compuesto de fórmula (I) + Piretrum. Reivindicaciones 1-6.
44. Compuesto de fórmula (I) + Bupofezina. Reivindicaciones 1-6.
45. Compuesto de fórmula (I) + Pirifluquinazona. Reivindicaciones 1-6.
46. Compuesto de fórmula (I) + Espinetoram. Reivindicaciones 1-6.
47. Compuesto de fórmula (I) + Espinosad. Reivindicaciones 1-6.
48. Compuesto de fórmula (I) + Clorfenapir. Reivindicaciones 1-6.
49. Compuesto de fórmula (I) + Tebufenpirad. Reivindicaciones 1-6.
50. Compuesto de fórmula (I) + Abamectina. Reivindicaciones 1-6.
51. Compuesto de fórmula (I) + *Bacillus firmus* I-1582. Reivindicaciones 1-6.
52. Compuesto de fórmula (I) + Timol. Reivindicaciones 1-6.
53. Compuesto de fórmula (I) + *Metarhizium anisopliae* cepa F52. Reivindicaciones 1-6.
54. Compuesto de fórmula (I) + *Bacillus pumilus* cepa QST2808. Reivindicaciones 1-6. . Reivindicaciones 1-6.
55. Compuesto de fórmula (I) + *Bacillus thuringiensis* spp aizawai. . Reivindicaciones 1-6.

56. Compuesto de fórmula (I) + *Bacillus amyloliquefaciens* FZB42. Reivindicaciones 1-6.
57. Compuesto de fórmula (I) + *Bacillus subtilis* QST712. Reivindicaciones 1-6.
58. Compuesto de fórmula (I) + 1-(3-cloropiridin-2-il)-N-[4-ciano-2-metil-6-(metilcarbamoil)fenil]-3-[[5-(trifluorometil)-1H-tetrazol-1-il]metil]-1H-pirazol-5-carboxamida.

7. Determinación del Estado de la Técnica

El estado de la técnica se determinó con base en la fecha de presentación de la solicitud de la cual se invoca prioridad, es decir, diciembre 15 de 2011. Consultadas las fuentes de información con que se cuenta, se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Ítem	Documento	Título	Fecha de Publicación
D1	US20090076282	"3-Triazolylphenyl sulfide derivative and insecticide/acaricide/nematicide containing the same as active ingredient"	19/Marzo/2009
D2	US20110045104	"3-[1-(3-haloalquil)triazolyl] phenyl sulfide derivatives as acaricides and insecticides"	24/Febrero/2011

El documento D1⁽¹⁾ divulga combinaciones seguras con alto efecto pesticidas y bajo efecto residual conformadas por compuestos derivados de 3-triazolil-fenil-sulfido con compuestos con actividad insecticida, acaricida y nematocida, útiles en la prevención y/o tratamiento de la infestación por parte de insectos, ácaros y nematodos en plantas de granja o de jardín (Resumen; Pág. 1, [Párr. 0005] y Pág. 3, [Párrs. 0041-0042]).

El documento D2⁽²⁾ divulga composiciones seguras para las plantas y para los animales, tolerables por el medio ambiente y que mejoran los rendimientos de los cultivos conformadas por compuestos derivados de 3-haloalquil-triazolil-fenil-sulfido e insecticidas o acaricidas, útiles en el tratamiento de pestes de insectos y ácaros en plantas (Resumen; Pág. 1, [Párr. 0004]; Pág. 7, [Párr. 0030] y Pág. 9, [Párrs. 0056-0057]).

8. Examen de Patentabilidad (Art 14 D486)

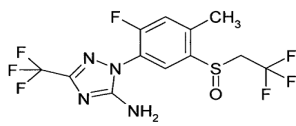
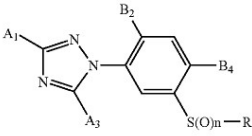
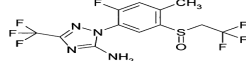
Novedad (Art 16 D486)

La reivindicación 1 consiste en una "Combinación de principios activos que comprende de la fórmula (I) y uno o más insecticidas y/o acaricidas y/o agentes de combate biológico (...)".

1. www.spacenet/US20090076282

2. www.spacenet/US20110045104

Comparación de las características técnicas esenciales, con las del estado de la técnica:

Características esenciales	D1
Combinaciones de principios activos que comprende:	Combinaciones de principios activos que comprende
Compuesto de fórmula (I) 	 A1=CF ₃ A3=NH ₂ B2=F R=CH ₂ CF ₃ n=1 Compuesto No 2  (Pág. 4, Tabla No 1 y Pág. 28, Ej. 5.)
Un insecticida o acaricida o agente de combate biológico	Insecticidas o acaricidas (Pág. 24, [Párr.0322])

De acuerdo con la tabla anterior, las características esenciales de la composición de la reivindicación 1 habían sido divulgadas previamente en el documento D1, por lo tanto, la materia reivindicada no es nueva.

En consecuencia, la reivindicación 1 carece de novedad, según lo divulgado en el documento D1.

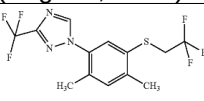
Las reivindicaciones dependientes 2-3 no mencionan alguna característica que haga nueva a la composición de la reivindicación 1, por lo cual se considera que no son nuevas.

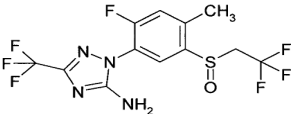
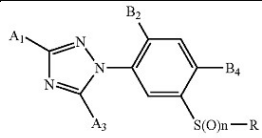
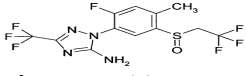
Nivel inventivo (Art18 D486)

El presente estudio de patentabilidad se hará sobre grupo inventivo N° 3: Compuesto de fórmula (I) + Clotianidina

La reivindicación 4 consiste en la “Combinación según cualquiera de las reivindicaciones 1 a 3, en las que el insecticida y/o acaricida y/o agente de combate biológico (II) se selecciona entre (...) clotianidina (...)”.

Comparación de las características técnicas esenciales, con las del estado de la técnica:

Características esenciales	D2	D1
Combinaciones de principios activos que comprende:	Composición que comprende (Pág. 34, Rv. 6)	Combinaciones de principios activos que comprende
Compuesto de fórmula (I)	 Compuesto VI-297	

	(Pág. 31, [0251])	 A1=CF3 A3=NH2 B2=F R=CH2CF3 n=1 Compuesto N° 2  (Pág. 4, Tabla No 1 y Pág. 28, Ej. 5.)
Insecticida (Clotianidina)	Insecticida (Clotianidina) (Pág. 10, [Párr.0079] y Pág. 34, Rv. 6)	Insecticidas (Clotianidina) (Pág. 24, [Párrs.0322 y 0326])

Los documentos D2 y D1 se consideran el estado de la técnica cercano a la invención definida en la reivindicación 4 porque en el caso del documento D2 divulga composiciones seguras para las plantas y para los animales, tolerables por el medio ambiente y que mejoran los rendimientos de los cultivos conformadas por compuestos derivados de 3-haloalquil-triazolil-fenil-sulfido e insecticidas o acaricidas, útiles en el tratamiento de pestes de insectos y ácaros en plantas (Resumen; Pág. 1, [Párr. 0004]; Pág. 7, [Párr. 0030] y Pág. 9, [Párrs. 0056-0057]).

Por su parte, el documento D1 divulga combinaciones seguras con alto efecto pesticidas y bajo efecto residual conformadas por compuestos derivados de 3-triazolil-fenil-sulfido con compuestos con actividad insecticida, acaricida y nematicida, útiles en la prevención y/o tratamiento de la infestación por parte de insectos, ácaros y nematodos en plantas de granja o de jardín (Resumen; Pág. 1, [Párr. 0005] y Pág. 3, [Párrs. 0041-0042]).

La diferencia entre la combinación, definida en la reivindicación 4 y la combinación revelada en el documento D2 consiste en que la combinación reclamada está conformada por el compuesto de fórmula (I) y clotianidina, mientras que la combinación divulgada en el documento D2 está constituida por el compuesto VI-297 con clotianidina.

El efecto que logra combinar el compuesto de fórmula (I) con clotianidina consiste en que se combate la infestación de insectos en plantas.

Por lo tanto, el problema técnico objetivo que pretende resolver esta invención se puede formular así: “cómo proporcionar combinaciones que comprendan al compuesto de fórmula (I) para combatir infestaciones de insectos en plantas”.

Sin embargo, la combinación del compuesto de fórmula (I) con clotianidina para combatir la infestación de insectos en plantas, está divulgada en el documento D1 que enseña combinaciones que contienen al compuesto N° 2 (correspondiente al compuesto de fórmula (I)) y clotianidina, las cuales son útiles en la prevención y/o

tratamiento de la infestación por parte de insectos, ácaros y nematodos en plantas de granja o de jardín (Resumen; Pág. 1, [Párr. 0005] y Pág. 3, [Párrs. 0041-0042]).

Además, es parte del conocimiento de la persona normalmente versada en la materia que la clotianidina es un insecticida agonista de los receptores post-sinápticos nicotínicos de acetilcolina sin que inhiba al AChE y que es aplicado en cultivos de acuerdo con lo divulgado en los documentos “Clothianidin”⁽³⁾ y “Pesticide Fact Sheet Clothianidin”⁽⁴⁾.

En consecuencia, la persona del oficio normalmente versada en la materia, incluiría en la combinación revelada en el documento D2 al compuesto No 2 (corresponde al compuesto de fórmula (I)) de acuerdo con lo divulgado en el documento D1, para llegar así al objeto de la reivindicación 4 de la solicitud. Por lo cual se considera obvia.

Puesto que las reivindicaciones dependientes 5-6 y 13 no mencionan características inventivas adicionales, tampoco se pueden considerar inventivas.

9. Conclusión

Los requisitos de Patentabilidad de la presente solicitud están afectados así:

Ítem	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	US20090076282	1-3 4-6 y 13	Novedad Nivel inventivo
D2	US20110045104	4-6 y 13	Nivel inventivo

3. http://ec.europa.eu/food/plant/protection/evaluation/newactive/list_clothianidin.pdf

4. http://www.epa.gov/pesticides/chem_search/reg_actions/registration/fs_PC-044309_30-May-03.pdf

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta (60) días contados a partir del día siguiente de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Se invita al solicitante se sirva indicar, si así lo considera, su renuncia al término faltante de sesenta (60) días para dar respuesta a este requerimiento y presentarla por escrito.

Finalmente, se le recuerda al solicitante que si como respuesta a este requerimiento llegara a modificar el capítulo reivindicatorio y éste contenga más de diez (10) reivindicaciones, no pagará la tasa de modificación voluntaria pero sí la correspondiente al pago por reivindicación adicional.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No. 10 de 2001.



JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista, de fecha 2015-05-19

Elaboró: German Antonio Clavijo Cohen
Revisó: Jeny Paola Villate Becerra



EUROPEAN COMMISSION
HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL

Directorate D - Food Safety: Production and distribution chain
Unit D.3 - Chemicals, contaminants and pesticides

Clothianidin

SANCO/10533/05 - Final

18 January 2005

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

Review report for the active substance **clothianidin**

Finalised in the Standing Committee on the Food Chain and Animal Health at its meeting on 27 January 2006 in view of the inclusion of clothianidin 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 clothianidin, 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 Belgian authorities received on 26 September 2001 an application from Sumitomo Chemical Takeda Agro Company Ltd. London, hereafter referred to as the applicant, for the inclusion of the active substance clothianidin in Annex I to the Directive. The Belgian authorities indicated to the Commission on 16 October 2001 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 clothianidin was distributed to the Member States and the Commission.

The Commission referred the dossier to the Standing Committee on the Food Chain and Animal Health in the meeting of the working group 'legislation' thereof on 27 November 2001, 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 2002/305/EC¹ of 19 April 2002 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 Belgium, as rapporteur Member State, would carry out the detailed examination of the dossier and report the conclusions of the 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.

Belgium submitted to the Commission on 04 June 2003 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 clothianidin in Annex I to the Directive.

On receipt of the draft assessment report, the Commission forwarded it for consultation to all the Member States as well as to Sumitomo Chemical Takeda Agro Company Ltd. London being the sole applicant on 12 June 2003.

The active substance was evaluated in the Co-rapporteur System, with the United Kingdom acting as Co-Rapporteur Member State. Further discussions between the Rapporteur Member State and the Co-rapporteur Member State were organised, to review the draft assessment report and the comments received thereon 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 evaluation between the Rapporteur Member State and the Co-rapporteur Member State took place from October 2003 to February 2004.

The report of the peer review (in this case the final reporting table) was circulated, for further consultation, to Member States and the sole applicant on 25 May 2004.

The dossier, revised draft assessment report and the peer review report including in particular an outline resumé of the remaining technical questions, were referred to the Standing Committee on

¹ OJ L 104, 20.4.2002, p.42.

the Food Chain and Animal Health, and specialised working groups of this Committee, for final examination, with participation of experts from all Member States. This final examination took place from May 2004 to September 2005, and was finalised in the meeting of the Standing Committee on 27 January 2006.

The present review report contains the conclusions of this final examination; given the importance of the revised draft assessment report, the peer review report and the comments and clarifications submitted after the revision of the draft assessment report 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.

The review of clothianidin did not reveal any open questions or concerns, which would have required a consultation of the Scientific Committee on Plants or of the European Food Safety Authority which has taken over the role of that Committee.

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 2006/41/EC² concerning the inclusion of clothianidin in Annex I to Directive 91/414/EEC, and to assist the Member States in decisions on individual plant protection products containing clothianidin 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.

² OJ L 187, 18.7.2006, p. 24.

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 clothianidin 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 clothianidin containing plant protection product for which Member States will grant or review the authorisation.

Furthermore, these conclusions were reached within the framework of the uses which were proposed and supported by the sole data submitter and mentioned in the list of uses supported by available data (attached as Appendix IV to this Review Report).

Extension of the use pattern beyond those 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. This may in particular be the case for the risk to honeybees and non-target arthropods for uses of clothianidin other than as a seed dressing as set out in Appendix IV to this Review Report.

4. Specific conclusions which are highlighted in this evaluation

4.1 Residues of clothianidin 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 0.00206 % of the Acceptable Daily Intake (ADI), based on the FAO/WHO European Diet (1998). This low intake value reflects the current limited use pattern for this active substance. The acute intake calculation was performed based on the ARfD value of 0.10 mg/kg bw/day. The national estimated short term intake (NESTI) for maize is 0.0417 % and 0.083 % of the ARfD respectively for adults and toddlers; and for sugar beet: 0.046 % and 2.58 % of the ARfD respectively for adults and toddlers.

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 also concluded that under the proposed and supported conditions of use there are no unacceptable effects on the environment, as provided for in Article 4 (1) (b) (iv) and (v) of Directive 91/414/EEC, provided that certain conditions are taken into account as detailed in section 7 of this report.

5. Identity and Physical/chemical properties

The main identity and the physical/chemical properties of clothianidin 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 (Sumitomo Chemical Takeda Agro Company Ltd. London), none of the manufacturing impurities considered are, on the basis of information currently available, of toxicological or environmental concern.

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 clothianidin

On the basis of the proposed and supported uses, the following particular issues have been identified as requiring particular and short term (within 12 months at the latest) attention from the Member States, in the framework of any authorisations to be granted, varied or withdrawn, as appropriate:

Member States

- must pay particular attention to the protection of groundwater, when the active substance is applied in regions with vulnerable soil and/or climate conditions;
- must pay particular attention to the risk to granivorous birds and mammals when the substance is used as a seed dressing.

Conditions of use shall include risk mitigation measures, where 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 clothianidin in Annex I.

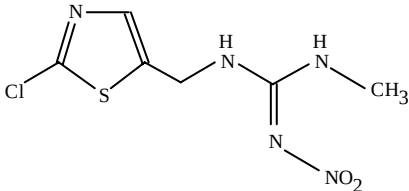
9. Updating of this review report

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 the Food Chain and Animal Health, in connection with any amendment of the inclusion conditions for clothianidin in Annex I of the Directive.

APPENDIX I

Identity, physical and chemical properties

CLOTHIANIDIN

Common name (ISO)	Clothianidin
Development Code (for new actives only)	TI-435
Chemical name (IUPAC)	(E)-1-(2-chloro-1,3-thiazol-5-ylmethyl)-3-methyl-2-nitroguanidine
Chemical name (CA)	[C(E)]-N-[(2-chloro-5-thiazolyl)methyl]-N'-methyl-N''-nitroguanidine
CIPAC No	738
CAS No	210880-92-5
EEC No	not allocated
FAO SPECIFICATION	not available
Minimum purity	min. 960 g/kg (full scale manufacturing)
Molecular formula	C ₆ H ₈ ClN ₅ O ₂ S
Molecular mass	249.7 g/mol
Structural formula	

Melting point	176.8°C (99.7%)
Boiling point	Not applicable (not a low melting substance)
Appearance	clear and colourless powder, odourless (99.7%) dim yellow powder, odourless (97.6%)
Relative density	$D_4^{20} = 1.61$ (99.7%)
Vapour pressure	3.8×10^{-11} Pa at 20°C
Henry's law constant	2.9×10^{-11} Pa.m ³ .mol ⁻¹ at 20°C
Solubility in water	Milli-Q water : 0.327 g/L at 20°C
	pH 4: 0.304 g/L at 20°C
	pH 10: 0.340 g/L at 20°C
Solubility in organic solvents	solubility at 25°C in heptane : < 0.00104 g/L xylene : 0.0128 g/L dichloromethane : 1.32 g/L methanol : 6.26 g/L octanol : 0.938 g/L acetone : 15.2 g/L ethylacetate : 2.03 g/L
Partition co-efficient (log P_{ow})	pH 4: 0.893 at 25°C
	pH 7: 0.905 at 25°C
	pH 10: 0.873 at 25°C
Hydrolytic stability (DT₅₀)	pH 4 : stable at 50°C
	pH 7 : stable at 50°C
	pH 9 : 1401 d at 20°C
Dissociation constant	pKa = 11.09
Quantum yield of direct photo-transformation in water at $\lambda > 290$ nm	0.014
Flammability	not highly flammable
Explosive properties	not explosive
UV/VIS absorption (max.)	neutral conditions : $\lambda_{\max}$ 265.5 nm : $\epsilon = 1.71 \times 10^4$ L.mol ⁻¹ .cm ⁻¹ $\lambda_{\max}$ 214.5 nm : $\epsilon = 7.77 \times 10^3$ L.mol ⁻¹ .cm ⁻¹ at 290 nm : $\epsilon = 5350$ L.mol ⁻¹ .cm ⁻¹
Photostability in water (DT₅₀)	pH 7 : 3.3 hr at 25°C

APPENDIX II

END POINTS AND RELATED INFORMATION

CLOTHIANIDIN

1 Toxicology and metabolism

Absorption, distribution, excretion and metabolism in mammals

Rate and extent of absorption:	-oral: rapid (24h) and efficient (89-95%) -dermal: 2.25% (monkey study)
Distribution:	Widely distributed up to 72h, slight preference for kidney, liver, urinary bladder, adrenales
Potential for accumulation:	no evidence
Rate and extent of excretion:	Rapid, within 24h: 91% (low dose), 57% (high dose) in urine; <7% in faeces; limited enterohepatic circulation
Toxicologically significant compounds:	Clothianidin ^a , MG ^{p,ph} , TMG ^p ^a : animals, ^p : plants; ^{ph} : photolysis
Metabolism in animals:	Moderate metabolisation (urine, 72h, % of dose): 56-74% parent compound, 8-13% MNG, 7-11% TZNG, 9% MTCA, 1-4% NTG +9 metabolites <2% Oxydative demethylation and C-N cleavage between thiazolyl-nitroimino moiety

Acute toxicity

Rat LD ₅₀ oral:	500 mg/kg bw < LD50 < 2000 mg/kg bw
Rat LD ₅₀ dermal:	No data Rabbit LD ₅₀ dermal: >2000 mg/kg b.w./d
Rat LC ₅₀ inhalation:	>5.54 mg/l air
Skin irritation:	not irritant
Eye irritation:	not irritant
Skin sensitization (test method used and result):	not sensitizing

Short term toxicity

Target / critical effect:	haematopoietic organs (rat, dog); kidney (mouse)
Lowest relevant oral NOAEL / NOEL:	10 mg/kg bw/d (developmental toxicity rat: body weight gain decrease; developmental toxicity rabbit: clinical signs)
Lowest relevant dermal NOAEL / NOEL:	systemic NOAEL: 300 mg/kg bw/d (21 d rat: bw effects) local NOAEL >1000 mg/kg bw/d (21 d rat)
Lowest relevant inhalation NOAEL / NOEL:	not determined

Genotoxicity

In-vitro: pve in TK and CHL: clastogenic at cytotoxic doses; nve in Ames, HPRT
In-vivo: nve in mouse bone marrow and liver UDS

Long term toxicity and carcinogenicity

Target / critical effect:	interstitial ovarian gland hyperplasia, bw effects, feed consumption (2 yr rat)
Lowest relevant NOAEL:	9.7 mg/kg bw/d
Carcinogenicity:	none

Reproductive toxicity

Target / critical effect - Reproduction:	2G rat: slight stillborn pup incidence; slight sperm motility / morphology
Lowest relevant reproductive NOAEL / NOEL:	NOAEL <u>parental/pup toxicity</u> : 10 mg/kg bw/d (bw, thymus weight, preputial separation / vaginal patency) NOAEL <u>reproduction</u> : 32.7 mg/kg bw/d
Target / critical effect - Developmental toxicity:	Rabbit: absence intermediate lung lobe, ossification sternal centers
Lowest relevant developmental NOAEL / NOEL:	NOAEL <u>maternal</u> : 10 mg/kg bw/d (mortality, clinical signs) NOAEL <u>foetal</u> : 25 mg/kg bw/d (abortions, premature deliveries, foetal weight) NOAEL <u>reproduction</u> : 25 mg/kg bw/d

Delayed neurotoxicity

-Delayed neurotoxicity not required
 -Acute neurotoxicity: 60 mg/kg bw/d (locomotor activity, hypothermia)
 -Short-term neurotoxicity NOAEL: 177 mg/kg bw/d
 -neurodevelopmental toxicity NOAEL:
 43 mg/kg bw/d (startle habituation, motor activity, surface righting, brain histometry findings)

Other toxicological studies

Metabolite data:
 Livestock/plant/environmental metabolites more toxic than Clothianidin, but occur at very low residue levels or present in the rat, thus toxicologically covered.

Investigation on enzyme induction:
 Slight enzymatic induction potential in the liver; no influence on thyroid hormone activity (T₃, T₄, TSH) in 90d rat study.

Pharmacological studies:
 Effects consistent with nicotinic CNS-stimulation and depression
 (impaired pupillar function, deep respiration, hypothermia, increased heart rate, hypotension)

Medical data

No data: new compound

Summary

	Value	Study	Safety factor
ADI:	0.097 mg/kg bw/d	2 yr rat, oral	100
AOEL systemic:	0.10 mg/kg bw/d	developmental toxicity rat and rabbit	100
AOEL inhalation:	Not relevant		
AOEL dermal:	Not relevant		
ARfD (acute reference dose):	0.10 mg/kg bw/d	developmental toxicity rat and rabbit	100

Dermal absorption

2.25% (in-vivo monkey study)

2 Fate and behaviour in the environment

2.1 Fate and behaviour in soil

Route of degradation

Aerobic:

Mineralization after 100 days:

1.5-11.2 % after 120 days (10 soils)

Non-extractable residues after 100 days:

1.9-9.9 % after 120 days (10 soils)

Major metabolites above 10 % of applied active substance: name and/or code
% of applied rate (range and maximum)

TZNG : 9.1% after 120 days (4 soils)
MNG : 10.7% after 120 days (4 soils)

Supplemental studies

Anaerobic:

water/sediment system :
no mineralisation : < 0.1%
max. level bound residues : 82.6% at day 182
each individual metabolite < 5%

Soil photolysis:

Mineralisation : 4.5 % at day 17
Max level bound residues : 36.8% at day 17
Each individual metabolite (TZNG, TZMU, MNG, U1-U6) < 4.4%

DT_{50lab} (20°C, irradiation) : 8.2 days equivalent to 34 days, June natural summer sunlight at 40°N.
(R² = 0.9729)

DT_{50lab} (20°C, dark condition) : 183 days (R² = 0.8315)

DT_{90lab} (20°C, irradiation) : 27 days
DT_{90lab} (20°C, dark condition) : > 1 year

Remarks:

none

Rate of degradation

Laboratory studies

DT_{50lab} (20 °C, aerobic):

DT_{90lab} (20 °C, aerobic):

DT_{50lab} (10 °C, aerobic):

DT_{50lab} (20 °C, anaerobic):

First order kinetics (lab and field studies)
DT _{50lab} (a.s., 20°C, aerobic): 143-1001 days, median = 545 days (10 soils, R ² = 0.7176-0.9987)
DT _{50lab} (MNG, 20°C, aerobic): 82.4-108 days, median = 86.4 days (3 soils, R ² = 0.865-975)
DT _{50lab} (TZNG, 20°C, aerobic): 62.1-111 days, median = 89.8 days (3 soils, R ² = 0.913-0.957)
DT _{50lab} (NTG, 20°C, aerobic): 57-95 days, median = 59 days (3 soils)
DT _{90lab} (a.s., 20°C, aerobic): > 1000 days (10 soils)
DT _{90lab} (MNG, 20°C, aerobic): 274-359 days, median = 287 days (3 soils)
DT _{90lab} (TZNG, 20°C, aerobic): 206-368 days, median = 298 days (3 soils)
DT _{90lab} (NTG, 20°C, aerobic): 188-315 days, median = 196 days (3 soils)
DT _{50lab} (10°C, aerobic): not required, field studies at relevant temperatures are available
DT _{50lab} (20°C, anaerobic, water/sediment): 21 days
degradation in the saturated zone: not required, anaerobic degradation data available

Field studies (country or region)

DT_{50f} from soil dissipation studies:

DT_{90f} from soil dissipation studies:

Soil accumulation studies:

DT _{50f} converted to 20°C, 8 locations in Germany, Great Britain, France, Spain, 6 bare soils and 2 cropped areas : 13.3-305.4 days, median = 156 days, geo. mean = 120.1 days
DT _{90f} converted to 20°C, 8 locations in Germany, Great Britain, France, Spain, 6 bare soils and 2 cropped areas : 44.2-1017.9 days, median = 517 days
4 field trials in Southern France, Germany and Great Britain, a.s. applied as seed dressing at 0.15 kg a.s./ha/year. Maximum concentrations in soil on a period of 1.5 –2.5 years (depending on the fields): Burscheid (GE), 34.8 µg a.s./kg soil at day 882, 10-20 cm depth St Etienne du Gres (FR), 40.8 µg a.s./kg soil at day 120, 0-10 cm depth Wellesbourne (UK), 37.0 µg a.s./kg soil at day 547, 0-10 cm depth MNG and TMG < 5 µg/kg soil

Clothianidin

APPENDIX II

END POINTS AND RELATED INFORMATION

2. Fate and behaviour in the environment

08 November 2005

Soil residue studies:

Not required

Remarks:

e.g. effect of soil pH on degradation rate

Not relevant

Adsorption/desorption

K_f / K_{oc} :

K_d :

K_{oc} (a.s.) : 84-345 (mean = 160, median = 123, $1/n = 0.8088-0.8648$, 5 soils)

K_{oc} (MNG) : 5.2-34.3 (mean = 20.5, $1/n = 0.7017-1.1012$, 5 soils)

K_{oc} (TZNG) : 204.5-432.5 (mean = 275.4, $1/n = 0.7832-0.9010$, 5 soils)

K_{oc} (TZMU) : 46.4-95.8 (mean = 61.8, $1/n = 0.8430-0.9276$, 5 soils)

K_{oc} (TMG) : 525-3620 (mean = 2459, $1/n = 0.7297-0.8493$, 5 soils)

K_{oc} (TNG) : 13.8-17.3 (mean = 16.0, $1/n = 0.87-0.88$, 3 soils)

no

pH dependence:

Mobility

Laboratory studies:

Column leaching:

Aged residue leaching:

Not required

Not required

Field studies:

Lysimeter/Field leaching studies:

- 1 lysimeter, Germany,
seed treatment application of 100 g a.s./ha on
winter barley and 137 g a.s./ha on winter wheat,
860-912 mm annual rainfall
annual average concentration in the leachate:
0.013, 0.062 and 0.104 µg a.s. equivalent/l
respectively for the 1st, 2nd and 3rd years
a.s. not detected in the leachates.

- 2 lysimeters, Germany,
foliar application of 160 g a.s./ha on grass during
2 consecutive years, summer applications, 847-
930 mm annual rainfall.
annual average concentration in the leachate: in
the range 0.080-0.417 µg a.s. equivalent/l
depending on year and lysimeter
a.s. not detected in the leachates. MNG at
maximum level of 0.068 µg/l, NTG at maximum
level of 0.037 µg/l.

Remarks:

none

2.2 Fate and behaviour in water

Abiotic degradation

Hydrolytic degradation:

pH 4, 50°C: hydrolytically stable

pH 7, 50°C: hydrolytically stable

pH 9, 50°C: DT₅₀ = 14.4 d

pH 9, 20°C: DT₅₀ = 1401 d

Major metabolites:

No degradates at temperature of environmental concern (20°C)

Photolytic degradation:

xenon light with UV filter (cut off $\lambda < 290$ nm) ,at 25°C, phosphate buffer pH 7 (sterile conditions, cosolvent acetonitrile < 1%), continuous irradiation for 18 d:

DT₅₀ = 3.3 h (mean of 2 labels)

Major metabolites:

photolysis products > 10% of applied radioactivity:

TZMU : N-(2-chlorothiazol-5-ylmethyl)-N'-methylurea (35% after 24 h; 23% after 18 d)

MG : methylguanidine (35% after 18 d)

HMIO : 4-hydroxy-2-methylamino-2-imidazolin-5-one (27% after 24 h; 7% after 18 d)

FA : formamide (16% after 5 d, 14% after 18 d)

MU : methylurea (11% after 18 d)

CO₂ (34% after 18 d in thiazolyl study)

Biological degradation

Readily biodegradable:

Not readily biodegradable

Water/sediment study:

DT₅₀ water:

30.8-49.8 days

DT₉₀ water:

not determined

DT₅₀ whole system:

48.0-64.8 days

DT₉₀ whole system:

not determined

Distribution in water / sediment systems (active substance)

Water : max. level of 92.3% at day 0,
Sediment : max. level of 37.3% at day 7

Distribution in water / sediment systems (metabolites)

Water : No metabolite detected
Sediment : TMG at max. level of 22.9% at day 58

Accumulation in water and/or sediment:

No accumulation

Degradation in the saturated zone

-

Remarks:

none

2.3 Fate and behaviour in air

Volatility

Vapour pressure:

3.8×10^{-11} Pa at 20°C

Henry's law constant:

2.9×10^{-11} Pa.m ³ .mol ⁻¹ at 20°C
--

Photolytic degradation

Direct photolysis in air:

Not required

Photochemical oxidative degradation in air

DT₅₀:

DT ₅₀ in troposphere = 1 h, corresponding to chemical lifetime τ of 1.4 h (using a 12 h day with 1.5×10^6 OH radicals/cm ³)
--

Volatilisation:

from plant surfaces: not required

from soil: not required

Remarks:

none

3 Ecotoxicology

Terrestrial Vertebrates

Acute toxicity to mammals:

Acute toxicity to birds:

Dietary toxicity to birds:

Reproductive toxicity to birds:

Short term oral toxicity to mammals:

LD₅₀ (mice) = 389 mg a.s./kg bw

LD₅₀ (Japanese quail) = 430 mg a.s./kg bw

LC₅₀ (mallard duck) > 752 mg a.s./kg bw

NOEC (bobwhite quail) = 56.8 mg a.s./kg bw

NOAEL (28 d) (mice) = 190 mg a.s./kg bw

Aquatic Organisms

Acute toxicity fish:

Long term toxicity fish:

Bioaccumulation fish:

Acute toxicity invertebrate:

Chronic toxicity invertebrate:

Acute toxicity algae:

Acute toxicity sediment dwelling organism:

Chronic toxicity sediment dwelling organism:

Group	Test substance	Time-scale	Endpoint	Toxicity
Laboratory tests				
Oncorhynchus mykiss	clothianidin	Acute (96 h)	LC ₅₀	> 104.2 mg/L
Pimephales promelas	clothianidin	Long term (28 d)	NOEC	20 mg/L
Not required; log Pow < 3				
Daphnia magna	clothianidin	Acute (48 h)	LC ₅₀	> 40 mg/L
Daphnia magna	clothianidin	Long term (21 d)	NOEC	0.12 mg/L
Selenastrum capricornutum	clothianidin	Acute (96 h)	E _b C ₅₀	55 mg/L
Chironomus riparius	clothianidin	Acute (48 h)	EC ₅₀	0.029 mg/L
Chironomus riparius	clothianidin	Long term (28 d)	EC ₁₅ =	0.72 x 10 ⁻³ mg/L
Microcosm or mesocosm tests				
EAC = 3.1 µg a.s./L				

Honeybees

Acute oral toxicity:

Acute contact toxicity:

LD₅₀ = 0.00379 µg a.s./bee

LD₅₀ = 3.9 µg TZNG/bee

LD₅₀ = 0.04426 µg a.s./bee

Other arthropod species

<i>Test species</i>	Stage	Test Substance	Dose	Endpoint	% Effect
Laboratory tests					
<i>Aphidius rhopalosiphi</i>	adult	clothianidin	60 g a.s./ha	Mortality	100%
<i>Typhlodromus pyri</i>	adult	Clothianidin 50% WDG	60 g a.s./ha	Mortality Fertility	96.7%
<i>Aleochara bilineata</i>	adult	Clothianidin 50% WDG	75 g a.s./ha	Mortality Fertility	99.99%
<i>Chrysoperla carnea</i>	adult	Clothianidin 50% WDG	60 g a.s./ha	Mortality Fertility	97%
Extended laboratory tests					
<i>Aphidius rhopalosiphi</i>	adult	Clothianidin 50% WDG	0.12-10 g a.s./ha	LR ₅₀ NOEC	1.086 g a.s./ha 0.37 g a.s./ha
<i>Trichogramma cacoeciae</i>	adult	Clothianidin 50% WDG	0.05-3 g a.s./ha	LR ₅₀ NOER	0.36 g a.s./ha 0.14 g a.s./ha
<i>Pardosa spp</i>	adult	Clothianidin FS 600	166 g a.s./ha maize	Mortality Feeding	6.3%
<i>Pardosa spp</i>	adult	Clothianidin FS 600	65 g a.s./ha rape seed	Mortality Feeding	-1%
<i>Pardosa spp</i>	adult	Clothianidin FS 600	140 g a.s./ha sugar beet	Mortality Feeding	13.4%
<i>Pardosa spp</i>	adult	Clothianidin FS 600	70 g a.s./ha sunflower	Mortality Feeding	21%
<i>Pardosa spp</i>	adult	Clothianidin FS 600	167 g a.s./ha barley	Mortality Feeding	1.4%
<i>Poecilus cupreus</i>	adult	Clothianidin 50% WDG	15-75 g a.s./ha	LR ₅₀	> 75 g as./ha
<i>Poecilus cupreus</i>	adult	Clothianidin FS 600	462 g a.s./ha maize	Mortality Feeding	23.3%

<i>Test species</i>	Stage	Test Substance	Dose	Endpoint	% Effect
Poecilus cupreus	adult	Clothianidin FS 600	59 g a.s./ha rape seed	Mortality Feeding	33.83%
Poecilus cupreus	adult	Clothianidin FS 600	488 g a.s./ha sugar beet	Mortality Feeding	-14%
Poecilus cupreus	adult	Clothianidin FS 600	269 g a.s./ha sunflower	Mortality Feeding	29%
Poecilus cupreus	adult	Clothianidin FS 600	149 g a.s./ha barley	Mortality Feeding	16.19%
Poecilus cupreus	larvae	Clothianidin FS 600	467 g a.s./ha maize	Mortality	100%
Poecilus cupreus	larvae	Clothianidin FS 600	96 g a.s./ha rape seed	Mortality	97%
Poecilus cupreus	larvae	Clothianidin FS 600	162 g a.s./ha sugar beet	Mortality	65%
Poecilus cupreus	larvae	Clothianidin FS 600	488 g a.s./ha sugar beet	Mortality	47%
Poecilus cupreus	larvae	Clothianidin FS 600	269 g a.s./ha sunflower	Mortality	93%
Poecilus cupreus	larvae	Clothianidin FS 600	181 g a.s./ha barley	Mortality	97%
Poecilus cupreus	larvae (aged residue)	Clothianidin FS 600	73.8 µg a.s./kg dry soil	Mortality	13%
Aleochara bilineata	adult	Clothianidin FS 600	467 g a.s./ha maize	Mortality Fecundity	72%
Aleochara bilineata	adult	Clothianidin FS 600	105 g a.s./ha rape seed	Mortality Fecundity	92%
Aleochara bilineata	adult	Clothianidin FS 600	157 g a.s./ha sugar beet	Mortality Fecundity	18%

<i>Test species</i>	Stage	Test Substance	Dose	Endpoint	% Effect
<i>Aleochara bilineata</i>	adult	Clothianidin FS 600	488 g a.s./ha sugar beet	Mortality Fecundity	77%
<i>Aleochara bilineata</i>	adult	Clothianidin FS 600	269 g a.s./ha sunflower	Mortality Fecundity	29%
<i>Aleochara bilineata</i>	adult	Clothianidin FS 600	130 g a.s./ha barley	Mortality Fecundity	89.45%
<i>Aleochara bilineata</i>	adult	Clothianidin	100-250 µg a.s./kg dry soil	LR ₅₀ NOEC	> 250 µg a.s./kg = 150 µg a.s./kg
<i>P. cupreus</i>	larvae	Clothianidin	0.02-0.08 mg a.s./kg dry soil	LR ₅₀ NOEC	= 0.046 µg a.s./kg = 0.02 µg a.s./kg
Semifield tests					
<i>Typhlodromus pyri</i>	adult	Clothianidin 50% WDG	9-150 g a.s./ha	LR ₅₀	125.99 g a.s./ha
<i>Aleochara bilineata</i>	adult	Clothianidin FS 600	168 g a.s./ha barley	Mortality Fecundity	-22%
<i>P. cupreus</i>	larvae	Clothianidin FS 600	25 g a.s./unit, 100000 seeds/ha or 2 units/ha)	Reduction of survival rate	20%
Field or semi-field tests Two field tests in winter wheat are available.					

Earthworms

Acute toxicity:

LC₅₀ = 13.21 mg a.s./kg soil

LC₅₀ = 970 mg TZNG/kg soil

Reproductive toxicity:

Study is not acceptable.

Not required as a field study is available (no treatment-related effects up to 225 g a.s./ha)

Soil micro-organisms

Nitrogen mineralization:

No effects up to 750 g a.s./ha

Carbon mineralization:

No effects up to 750 g a.s./ha

APPENDIX III

CLOTHIANIDIN

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

B.1 Identity, B.2 Physical and chemical properties, B.3 Data on application and further information, B.4 Proposals for classification and labelling, 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
IIA, 1.11/08 (Doc. J)	Beeck, S.	2004a	Material accountability of TI 435 A techn./clothianidin - Analytical profile of process samples. Bayer CropScience AG, report no. 15-920-2215 March 10, 2004 GLP, unpublished
IIA, 1.11/09 IIA, 1.8/01 IIA, 1.9/02 IIA, 1.10/03 (Doc. J)	Riegner, K.	2004	Impurity profiles of clothianidin technical. Bayer CropScience AG September 8, 2004 non GLP, unpublished
IIA, 1.11/10 (Doc. J)	Kramer, H.T.	2004a	Five lot analysis of TI-435 technical. Covance, USA, report no. 6155-139 SumiTake, report no. DPCI087 September 30, 2004 GLP, unpublished
IIA, 1.11/11 IIA, 4.1.2/ 07 (Doc. J)	Kramer, H.T.	2004b	Method validation for the determination of "TAK 13" in TI-435 technical. Covance, USA, report no. 6155-140 SumiTake, report no. DPCI088 September 30, 2004 GLP, unpublished
IIA, 1.11/12 (Doc. J)	Kramer, H.T.	2004c	Nitrosamine analysis of five lots of TI-435 technical. Covance, USA, report no. 6155-142 SumiTake, report no. DPCI089 September 30, 2004 GLP, unpublished
IIA, 1.11/13 IIA, 1.9/01 IIA, 1.10/02 (Doc. J)	Akayama, A.	2005	New specification for clothianidin technical material. Sumitomo Chemical Takeda Agro January 6, 2005 Non-GLP, unpublished

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
IIA, 1.11/14 (Doc. J)	Feldhues, E.	2005a	Determination of nitrosamines in TI 435 A techn./clothianidin. Amendment no. 1 Bayer AG, report no. G 05/0028/00 LEV May 23, 2005 GLP, unpublished
IIA, 1.11/15 (Doc. J)	Keppler, J.	2005	Ecotoxicological evaluation of clothianidin impurities "BAY 1", "BAY 3" and "BAY 4". Bayer CropScience AG March 30, 2005 Non-GLP, unpublished
IIIA, 2.5.2/ 02	Guedner, W.	2004a	Viscosity of TI 435 FS 600 RED. Bayer CropScience AG, report no. 14 1050 5296 April 27, 2004 GLP, unpublished
IIIA, 2.7.1/ 03 IIIA, 2.7.3/ 02	Guedner, W.	2004b	Storage stability and shelf life of TI 0435 FS 600 red. [Packaging material: HDPE] Bayer CropScience AG, report no. 06568-0249 November 11, 2004 Non-GLP, unpublished
IIA, 4.1.2/ 08 (Doc. J)	Krämer, F.	2002	Determination of volatile solvents in active ingredient of agrochemicals - GLC - internal standard (headspace). Bayer CropScience, report no. 2005-0013102-02 October 18, 2002 Non-GLP, unpublished
IIA, 4.1.2/ 09 (Doc. J)	Krämer, F.	2005	Validation of GLC-method 2005-0013102-02 - Determination of volatile solvents in active ingredient of agrochemicals, GLC - internal standard headspace - Specific solvent: "BAY 4", specific matrix: clothianidin (TI 435) Bayer CropScience, report no. VB1.8-2005-0013102 April 26, 2005 Non-GLP, unpublished
IIA, 4.1.2/ 10 (Doc. J)	Wanner, B.	2000	Analytical procedure for the argentometric determination of "BAY 6". Bayer AG, report no 2005-0000703-00 May 5, 2000 Non-GLP, unpublished
IIA, 4.1.2/ 11 (Doc. J)	Schröder, S.	2000	Validation report VB1-2005-0000703-00 E - Argentometric determination of "BAY 6". Bayer AG, report no. VB1-2005-0000703 May 9, 2000 Non-GLP, unpublished
IIA, 4.1.2/ 12 (Doc. J)	Beeck, S.	2003a	TI 435 A - Quantification of by-products by HPLC - internal standard. Analytical method 2005-0012602-03 E Bayer CropScience, report no. MO-03-004132 February 21, 2003 Non-GLP, unpublished
IIA, 4.1.2/13 (Doc. J)	Beeck, S.	2003b	Validation of HPLC-method 2005-0012602-03 - By-products of TI435 technical A, HPLC - internal standard. Bayer CropScience, report no. VB1-2005-0012602 February 18, 2003 Non-GLP, unpublished

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
IIA, 4.1.2/ 14 (Doc. J)	Beeck, S.	2004b	TI 435 A - Quantification of by-products by HPLC - internal standard. Bayer CropScience, report no. 2005-0012603-04 June 8, 2004 Non-GLP, unpublished
IIA, 4.1.2/ 15 (Doc. J)	Beeck, S.	2004c	Validation of HPLC-method 2005-0012603-04 - By-products of TI435 technical A, HPLC - internal standard. Bayer CropScience, report no. VB1-2005-0012603 June 8, 2004 Non-GLP, unpublished
IIA, 4.1.2/ 16 (Doc. J)	Beeck, S.	2005	TI 435: HPLC-method 2005-0012603-04 - TI 435 A technical - byproducts HPLC internal standard - Separation of "BAY 2" and "BAY 3". Bayer CropScience AG April 21, 2005 Non-GLP, unpublished
IIA, 4.1.2/ 17 (Doc. J)	Sporenberg, W. Wilms, A.	2001	Extraction of nitrosamines, including pentane extraction in product TI-435. Bayer, report no. MO-01-022140 November 16, 2001 Non-GLP, unpublished
IIA, 4.1.2/ 18 (Doc. J)	Feldhues, E.	2005b	Validation of an analytical method for the determination of N-nitrosamines in TI 435 A techn. clothianidin. Bayer AG, report no. 2011-0597101-01 D May 30, 2005 Non-GLP, unpublished

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
IIA, 5.1/ 02	Ohta, K.; Mikata, K.	2000	Determination of metabolites of TI-435 in major tissues of rats. Takeda Chemical Industries, Ltd., Tokyo, Japan, report no. 110286 December 20, 2000 GLP, unpublished
IIA, 5.8.1/ 18	Brown, L.D; Wheeler, C.R.; Korte, D.W.	1988	Acute oral toxicity of nitroguanidine in male and female rats. US Army Medical Research and Development Command, report no. 264 March 1988 Non-GLP, unpublished
IIA, 5.8.1/ 19	Krötlinger	1992	Nitroguanidine - summary assessment of toxicological data Bayer AG, report MO-02-013556 May 1992 Non-GLP, unpublished
IIA, 5.8.1/ 20	Coppes, V.G.; Gomez, C.L.; Magnuson, D.K.; Korte, D.W.	1988	Developmental toxicity potential of nitroguanidine in rabbits. Letterman Army Institute of Research, Presidio of San Francisco, California, USA. Institute report no. 298 September 1988 Non-GLP, published

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
IIA, 5.8.2/ 13	Krötlinger, F.	2000b	"BAY 3" - Acute oral toxicity study in male and female Wistar rats. Bayer AG, report no. PH 30096 August 1, 2000 GLP, unpublished
IIA, 5.8.2/ 14	Herbold, B.	2000c	"BAY 3" - <i>Salmonella</i> /microsome test - Plate incorporation and preincubation method. Bayer AG, report no. PH 30172 August 23, 2000 GLP, unpublished
IIA, 5.8.2/ 15	Vohr, H.W.	2000b	"BAY 3" - Study for the skin sensitization effect in guinea pigs. Bayer AG, report no. PH 30219 September 4, 2000 GLP, unpublished
IIA, 5.8.2/ 16	Leuschner, J.	2000a	Acute eye irritation study of "BAY 3" by instillation into the conjunctival sac of rabbits. LPT Laboratory, report no. 9301/423/95 Bayer AG, report no. R 7805 May 8, 2000 GLP, unpublished
IIA, 5.8.2/ 17	Leuschner, J.	2000c	Acute skin irritation test (patch test) of "BAY 3" in rabbits. LPT Laboratory, report no. 9300/423/95 Bayer AG, report no. R 7804 April 28, 2000 GLP, unpublished
IIA, 5.8.2/ 18	Sokolowski, A.	2003	<i>Salmonella typhimurium</i> reverse mutation assay. RCC-CCR GmbH, Germany, report no. 803401 Bayer CropScience SA, report no. MO-03-015766 December 3, 2003 GLP, unpublished
IIA, 5.8.2/ 19	Poth, A.	2003	Gene mutation assay in Chinese hamster V79 cells <i>in vitro</i> (V79/HPRT) with TI-435. RCC-CCR GmbH, Germany, report no. 803402 Bayer CropScience SA, report no. MO-03-015743 December 9, 2003 GLP, unpublished
IIA, 5.8.2/ 20	Schulz, M.	2003	<i>In vitro</i> chromosome aberration test in Chinese hamster V79 cells with TI-435. RCC-CCR GmbH, Germany, report no. 803403 Bayer CropScience SA, report no. MO-03-015744 December 9, 2003 GLP, unpublished
IIA, 5.8.2/ 21	Honarvar, N.	2003a	Micronucleus assay in bone marrow cells of the mouse with TI-435. RCC-CCR GmbH, Germany, report no. 803404 Bayer CropScience SA, report no. MO-03-015745 December 10, 2003 GLP, unpublished
IIA, 5.8.2/ 22	Honarvar, N.	2003b	<i>In vivo/in vitro</i> unscheduled DNA synthesis in rat hepatocytes with TI-435. RCC-CCR GmbH, Germany, report no. 803405 Bayer AG, report no. MO-03-015747 December 9, 2003 GLP, unpublished

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
IIA, 5.8.2/ 23	Wanner, B.; Heimann, K.G.	2005	Clothianidin technical - genotoxicological testing. Bayer CropScience AG June 1, 2005 Non-GLP, unpublished

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
None			

B.8 Environmental fate and behaviour

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Repo.rt No. GLP or GEP status (where relevant) Published or not
IIA, 7.1.1.2.1/ 05	Fliege, R.	2004a	[¹⁴ C]-Nitroguanidine: Aerobic soil degradation in three soils. Bayer CropScience AG, report no. MEF-04/220 SumiTake, report no. DEFT045 June 28, 2004 GLP, unpublished
IIA, 7.1.1.2.2/ 05	Peters, B.	2004	Determination of the residues of TI-435 (600 FS) in/on soil and winter wheat in Germany, southern France and Great Britain. 1. Interim Report Bayer CropScience AG, report no. MEF-04/206 SumiTake, report no. DEFT047 April 30, 2004 GLP, unpublished
IIA, 7.1.2/07	Fliege, R.	2004b	[¹⁴ C]-Nitroguanidine: Adsorption/desorption on three soils. Bayer CropScience AG, report no. MEF-04/219 SumiTake, report no. DEFT046 June 23, 2004 GLP, unpublished
IIIA, 9.2.1/ 03	Hammel, K.; Bingemann, R.	2004a	Predicted environmental concentrations of clothianidin (TI-435) and its metabolites in ground water recharge based on calculations with FOCUS-PEARL considering kinetic sorption. Bayer CropScience AG, report no. MEF-04/338 October 5, 2004 Non-GLP, unpublished
IIIA, 9.2.3/ 02	Hammel, H.; Bingemann, R.	2004b	Predicted environmental concentrations of clothianidin (TI-435) and its metabolites in surface water and sediment. Bayer CropScience AG, report no. MEF-04/320 August 2, 2004 Non-GLP, unpublished

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
IIIA, 10.1.2/ 05	Wolf, Ch.	2005	Generic field monitoring of birds and mammals on maize and beet fields in Austria. Bayer CropScience AG, report no. WFC/FS017 January 20, 2005 GLP, unpublished
IIIA, 10.3/ 13	Wolf, Ch.; Fülling, O; Wilkins, S.	2003	Field monitoring of small mammals on maize fields drilled with Mesuroi FS 500 dressed seeds in Germany. Bayer CropScience AG, report no. WFC/FS 06 February 6, 2003 GLP, unpublished
IIIA, 10.5.2/ 03	Maus, Ch.	2003	Evaluation of the effects of aged residues of TI 435 FS 250 on larvae of carabid beetles (<i>Poecilus cupreus</i>) under extended laboratory test conditions. Bayer CropScience AG, report no. Maus/PCL003 February 5, 2003 GLP, unpublished
IIIA, 10.5.2/ 04	Neumann, P.	2004	Evaluation of the effects on <i>Poecilus cupreus</i> larvae after the drilling of maize seeds dressed with TI-435 FS 600 in a semi-field study. Bayer CropScience AG, report no. NNP/PC022 March 16, 2004 GLP, unpublished

APPENDIX IV

List of uses supported by available data

Clothianidin

Crop and/or situation (a)	Member State or Country	Product name	F G or I (b)	Pests or Group of pests controlled (c)	Formulation		Application				Application rate per treatment			PHI (days) (l)	Remarks: (m)
					Type (d-f)	Conc. of as (i)	method kind (f-h)	growth stage & season (j)	number min max (k)	interval between applications (min)	kg as/ha min max	mg as/seed min max	kg as/ha min max		
Sugar beet / Fodder beet	EU - N EU – S	TI-435 FS 600	F	sucking and biting insects	FS	600 g/L	seed treatment	BBCH 00	1	n.a.	n.a.	0.15 – 0.6	0.0195 – 0.078	n.a.	-
Maize	EU - N EU - S	TI-435 FS 600	F	sucking and biting insects	FS	600 g/L	seed treatment	BBCH 00	1	n.a.	n.a.	0.5	0.050	n.a.	-

Remarks:

- (a) For crops, the EU and Codex classifications (both) should be used; where relevant, the use situation should be described (e.g. fumigation of a structure)
- (b) Outdoor or field use (F), glasshouse application (G) or indoor application (I)
- (c) e.g. biting and suckling insects, soil born insects, foliar fungi, weeds
- (d) e.g. wettable powder (WP), emulsifiable concentrate (EC), granule (GR)
- (e) GCPF Codes - GIFAP Technical Monograph No 2, 1989
- (f) All abbreviations used must be explained
- (g) Method, e.g. high volume spraying, low volume spraying, spreading, dusting, drench
- (h) Kind, e.g. overall, broadcast, aerial spraying, row, individual plant, between the plants - type of equipment used must be indicated

- (i) g/kg or g/l
- (j) Growth stage at last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including where relevant, information on season at time of application
- (k) The minimum and maximum number of application possible under practical conditions of use must be provided
- (l) PHI - minimum pre-harvest interval
- (m) Remarks may include: Extent of use/economic importance/restrictions

Clothianidin

APPENDIX IV

List of uses supported by available data

08 November 2005



Pesticide
Fact Sheet

Name of Chemical: Clothianidin
Reason for Issuance: Conditional Registration
Date Issued: May 30, 2003

1. **DESCRIPTION OF CHEMICAL**

Generic Name: (E)-1-(2-chloro-1,3-thiazol-5-ylmethyl)-3-methyl-2-nitroguanidine

Common Name: Clothianidin

Trade Name: Poncho 600

EPA Shaughnessy Code: 44309

Chemical Abstracts
Service (CAS) Number: 205510-53-8 205510-92-5 210880-92-5

Year of Initial
Registration: 2003

Pesticide Type: Insecticide

Chemical Family: Nitroguanidine subgroup of nicotinoids

U.S. Producer: Bayer Corporation

2. **USE PATTERNS AND FORMULATIONS**

Application Sites: Clothianidin is registered for seed treatment use on corn and canola.

Types of Formulations: 96% technical product
48% flowable concentrate end-use product

Types and Methods

of Application: For use in commercial liquid or slurry treaters by commercial treaters only.

Application Rates: Application rates for canola are 150 grams to 400 grams active ingredient per 100 kilograms of seed, equivalent to 0.01 to 0.024 pounds of active ingredient per acre. For corn, application rates are 0.25 to 1.25 milligram active ingredient per kernel. Based on a maximum planting rate of 35,000 seeds (kernels) per acre, the application rate for corn would be 8.8 to 44 grams active ingredient per acre, or approximately 0.02 to 0.1 pounds active ingredient per acre.

3. **SCIENCE FINDINGS**

Summary Science Statements

Based upon a battery of acute toxicity studies, Poncho 600 is classified as Toxicity Category III. Clothianidin is classified as a “not likely” human carcinogen. There are no to low concerns and no residual uncertainties with regard to pre- and/or postnatal toxicity from clothianidin, and the FQPA 10X Safety Factor has been removed. However, due to evidence of effects on the rat immune system and that juvenile rats appear to be more susceptible to these effects, and due to the lack of a developmental immunotoxicity study, a 10X database uncertainty factor is applied to all dietary exposure endpoints.

Available data indicate that clothianidin on corn and canola should result in minimal acute toxic risk to birds. However, assessments show that exposure to treated seeds through ingestion may result in chronic toxic risk to non-endangered and endangered small birds (e.g., songbirds) and acute/chronic toxicity risk to non-endangered and endangered mammals. Clothianidin has the potential for toxic chronic exposure to honey bees, as well as other nontarget pollinators, through the translocation of clothianidin residues in nectar and pollen. Clothianidin should not present a direct acute or chronic risk to freshwater and estuarine/marine fish, or a risk to terrestrial or aquatic vascular and nonvascular plants.

The fate and disposition of clothianidin in the environment suggest a compound that is a systemic insecticide that is persistent and mobile, stable to hydrolysis, and has potential to leach to ground water, as well as runoff to surface waters.

Chemical Characteristics

Property	Technical	End-use
Physical State	Solid powder	Liquid suspension
Color	Colorless	
Odor	Odorless	Latex paint like odor
Melting Point	176.8°C	
Density	1.61 g/mL @ 20°C	1.2632 g/ml
Solubility (Water)	0.327 g/L at 20°C	
Vapor Pressure	1.3×10^{-10} Pa @ 25°C	
Octanol/Water Partition Coefficient	$\text{Log } P_{\text{ow}} = 5$ @ 25°C	
pH	6.24 @ 23°C	

Toxicology Characteristics

Acute Toxicity of Clothianidin Technical			
Guideline No.	Study Type	Results	Toxicity Category
870.1100	Acute Oral - rat	$\text{LD}_{50} > 5000$ mg/kg	IV
870.1100	Acute Oral - mouse	$\text{LD}_{50} = 425$ mg/kg	II
870.1200	Acute Dermal - rat	$\text{LD}_{50} > 2000$ mg/kg	III
870.1300	Acute Inhalation - rat	$\text{LC}_{50} > 6.14$ mg/L	IV
870.2400	Primary Eye Irritation - rabbit	Mild conjunctivitis cleared within 24 hours	IV
870.2500	Primary Skin Irritation - rabbit	No irritation or dermal changes for the 3 days observed.	IV
870.2600	Dermal sensitization - guinea pig	Not a dermal sensitizer	N/A

Acute Toxicity of Poncho 600			
Guideline No.	Study Type	Results	Toxicity Category
870.1100	Acute Oral - rat	2000 mg/kg > LD ₅₀ > 500 mg/kg	III
870.1200	Acute Dermal - rat	LD ₅₀ > 4000 mg/kg	III
870.1300	Acute Inhalation - rat	LC ₅₀ > 1.8 mg/L	III
870.2400	Primary Eye Irritation - rabbit	No observed ocular irritation	IV
870.2500	Primary Skin Irritation - rabbit	No observed dermal irritation	IV
870.2600	Dermal sensitization - guinea pig	Not a dermal sensitizer	N/A

Subchronic, Chronic, and Other Toxicity	
Guideline No./ Study Type	Results
870.3100 90-Day oral toxicity rodents (rats)	NOAEL: 27.9/34.0 mg/kg/day (male/female) LOAEL: 202.0/254.2 mg/kg/day (male/female: decreased body weight and body weight gain).
870.3150 90-Day oral toxicity in nonrodents (dogs)	NOAEL: 19.3/42.1 mg/kg/day (male/female) LOAEL: 40.9/61.8 mg/kg/day (thinness, decreased body weight, body weight gain and anemia (one male); decreased white blood cells, albumin, and total protein (female)).
870.3200 21/28-Day dermal toxicity (rats)	NOAEL: 1000 mg/kg/day (highest dose tested) LOAEL: >1000 mg/kg/day
870.3700 Prenatal developmental in rodents (rats)	Maternal NOAEL: 10 mg/kg/day Maternal LOAEL: 40 mg/kg/day (decreased body weight gain and food consumption). Developmental NOAEL: 125 mg/kg/day Developmental LOAEL: cannot be established

Subchronic, Chronic, and Other Toxicity	
Guideline No./ Study Type	Results
870.3700 Prenatal developmental in nonrodents (rabbit)	Maternal NOAEL: 25 mg/kg/day Maternal LOAEL: 75 mg/kg/day (increased incidences of clinical signs (scant feces and orange urine), mortalities, decreased food consumption, early delivery, abortion, and decreased body weight gain) Developmental NOAEL: 25 mg/kg/day Developmental LOAEL: 75 mg/kg/day (premature deliveries, decreased gravid uterine weights, an increased litter incidence of a missing lobe of the lung and decreased litter average for ossified sternal centra per fetus).
870.3800 Reproduction and fertility effects (rat)	Parental systemic NOAEL: 31.2/36.8 mg/kg/day (male/female) Parental systemic LOAEL: 163.4/188.8 mg/kg/day (male/female) (decreased body weight, body weight gain and absolute and relative thymus weights). Offspring systemic NOAEL: 9.8/11.5 mg/kg/day (male/female) Offspring systemic LOAEL: 31.2/36.8 mg/kg/day (male/female: decreased body weight gains and delayed sexual maturation (male); decreased absolute thymus weights in F₁ pups of both sexes and an increase in stillbirths in both generations). Reproductive NOAEL: 31.2/188.8 mg/kg/day (male/female) Reproductive LOAEL: 163.4/not established mg/kg/day (male/female: decreased sperm motility, and increased number of sperm with detached heads in both generations).
870.4100 Chronic toxicity dogs	NOAEL: 46.4/40.1mg/kg/day (male/female) LOAEL: not established/52.9 mg/kg/day (male/female: clinical evidence of anemia in females). Note: dose-related decreases in ALT activity observed in mid- and high-dose males and females.
870.4200 Carcinogenicity mice	NOAEL: 171.4/65.1 mg/kg/day (male/female) LOAEL: 254.1/215.9 mg/kg/day (male/female: decreased body weight and body weight gain; decreased food consumption and food efficiency in males at the LOAEL). No evidence of carcinogenicity.

Subchronic, Chronic, and Other Toxicity	
Guideline No./ Study Type	Results
870.4300 Chronic feeding/Carcinogenicity rat	NOAEL: 82.0/32.5 mg/kg/day (male/female) LOAEL: 156.5/97.8 mg/kg/day (male/female, decreased body weight and food consumption and altered hepatocellular eosinophilic focus of the liver in both sexes; ovary interstitial gland hyperplasia and increased lymphohistiocytic infiltrate in females; and slightly increased incidences of pelvic mineralization and transitional cell hyperplasia in the kidney, mottled livers of males. No evidence of carcinogenicity.
870.5100 Gene Mutation bacterial reverse mutation assay Parent	Small, but significant increase in frequency of histidine revertants in TA1535 strain treated at 1500 and 5000 µg/plate +/-S9; still present but weaker in its absence. The positive response was only reproducible at 5000 µg/plate +/-S9. Clothianidin considered mutagenic under conditions of this test.
870.5100 Gene Mutation bacterial reverse mutation assay Parent	No mutagenic activity in bacteria (<i>Salmonella typhimurium</i> and <i>Escherichia coli</i>) under conditions of this assay.
870.5100 Gene Mutation bacterial reverse mutation assay Parent	No mutagenic activity in bacteria (<i>Salmonella typhimurium</i>) under conditions of this assay.
870.5100 Gene Mutation bacterial reverse mutation assay Parent	Only TA 1535 tested. No mutagenic activity in bacteria (<i>Salmonella typhimurium</i>) under conditions of this assay.
870.5100 Gene Mutation bacterial reverse mutation assay BN0335E2 metabolite	No mutagenic activity in bacteria (<i>Salmonella typhimurium</i>) under conditions of this assay.

Subchronic, Chronic, and Other Toxicity	
Guideline No./ Study Type	Results
870.5100 Gene Mutation bacterial reverse mutation assay TZMU metabolite	No mutagenic activity in bacteria (<i>Salmonella typhimurium</i>) under conditions of this assay.
870.5100 Gene Mutation bacterial reverse mutation assay methyl guanidine intermediate	No mutagenic activity in bacteria (<i>Salmonella typhimurium</i>) under conditions of this assay.
870.5100 Gene Mutation bacterial reverse mutation assay TZNG metabolite	No mutagenic activity in bacteria (<i>Salmonella typhimurium</i>) under conditions of this assay.
870.5100 Gene Mutation bacterial reverse mutation assay TMG metabolite	No mutagenic activity in bacteria (<i>Salmonella typhimurium</i>) under conditions of this assay.
870.5100 Gene Mutation bacterial reverse mutation assay BN0230M metabolite	No mutagenic activity in bacteria (<i>Salmonella typhimurium</i>) under conditions of this assay.
870.5100 Gene Mutation bacterial reverse mutation assay MAI metabolite	No mutagenic activity in bacteria (<i>Salmonella typhimurium</i>) under conditions of this assay.

Subchronic, Chronic, and Other Toxicity	
Guideline No./ Study Type	Results
870.5100 Gene Mutation bacterial reverse mutation assay N-Methylnitroguanidin intermediate	No mutagenic activity in bacteria (<i>Salmonella typhimurium</i>) under conditions of this assay.
870.5100 Gene Mutation - bacterial reverse mutation assay TI 435-Triazan intermediate	No mutagenic activity in bacteria (<i>Salmonella typhimurium</i>) under conditions of this assay.
870.5100 Gene Mutation - bacterial reverse mutation assay TI 435-CCMT-Adduct	No mutagenic activity in bacteria (<i>Salmonella typhimurium</i>) under conditions of this assay.
870.5300 Gene Mutation - <i>in vitro</i> mammalian cell gene mutation test (L5178Y TK +/- mouse lymphoma cells) Parent	Increases in mutant frequency with and without S9 at dose levels that were cytotoxic. The observed response was primarily due to small colony formation, indicating clastogenic activity.
870.5300 Gene Mutation - <i>in vitro</i> mammalian cell gene mutation test (V79-HPRT Assay) Parent	No increase in mutant frequency under the conditions of the study.

Subchronic, Chronic, and Other Toxicity	
Guideline No./ Study Type	Results
870.5395 Cytogenetics - mammalian erythrocyte micronucleus test Parent	Clothianidin is considered to be neither clastogenic nor aneugenic under these test conditions.
870.5375 Cytogenetics - <i>in vitro</i> mammalian chromosome aberration test (CHL Cells) Parent	Significant increases in frequency of cells with structural aberrations. Predominant types were chromatid breaks and exchanges. There was, however, no clear indication of a dose-related response in either the presence or absence of S9 activation.
870.5500 Other Effects - DNA Repair Test in <i>Bacillus subtillis</i> Parent	No potential for DNA damage under these conditions.
870.5550 Other Effects - (UDS) in Mammalian Cells in Culture Parent	No evidence (or a dose related positive response) that UDS was induced.
870.6200 Acute neurotoxicity screening battery (rat)	NOAEL: not established LOAEL: 100 mg/kg (FOB: decreased arousal and decreased motor and locomotor activity).
870.6200 Subchronic neurotoxicity screening battery (rat)	NOAEL: 60.0/71.0 mg/kg/day (male/female) LOAEL: 177.0/200.1 mg/kg/day (male/female:slightly decreased food consumption, body weights and body weight gains).

Subchronic, Chronic, and Other Toxicity	
Guideline No./ Study Type	Results
870.6300 Developmental neurotoxicity (rat)	Maternal NOAEL: 42.9 mg/kg/day Maternal LOAEL: 142 mg/kg/day (decreased body weights, body weight gains, and food consumption) Offspring NOAEL: 12.9 mg/kg/day Offspring LOAEL: 42.9 mg/kg/day (decreased body weights and body weight gains)
870.7485 Metabolism and pharmacokinetics (rat)	Overall recovery: 95-100%. Readily absorbed and excreted within 96 hours following a single 2.5 mg/kg bw or repeated oral dose of 25 mg/kg bw, but at a dose of 250 mg/kg, absorption became biphasic and was saturated.
870.7485 Metabolism and pharmacokinetics (mouse)	Of the administered radioactivity, 98.7-99.2% was recovered. Readily absorbed and excreted within 168 hours following a single oral dose of 5 mg/kg body weight.
870.7600 Dermal Penetration - monkey	Dermal absorption as the sum of urinary and fecal excretion and Cage/Pan/Chair Wash, Debris was 0.24 ($\pm$ 0.11) as percent of dose. Adjustment of the direct absorption determination was not necessary because recovery from the dermal dose was >90%. A value of 1% dermal absorption was considered appropriate for use in risk assessment. This estimation takes into account any variability that would have likely occurred with testing several dose levels.
Special Study: Neurotoxicity and pharmacology mouse	NOAEL: 25 mg/kg/day (male/female) LOAEL: 50 mg/kg bw mg/kg/day (transient signs of decreased spontaneous motor activity, tremors, and deep respirations).

Toxicological Endpoints

The dose at which no adverse effects are observed (the NOAEL) from the toxicology study identified as appropriate for use in risk assessment is used to estimate the toxicological level of concern (LOC). However, the lowest dose at which adverse effects of concern are identified (the LOAEL) is sometimes used for risk assessment if no NOAEL was achieved in the toxicology study selected. An uncertainty factor (UF) is applied to reflect uncertainties inherent in the extrapolation

from laboratory animal data to humans and in the variations in sensitivity among members of the human population as well as other unknowns. An UF of 100 is routinely used, 10X to account for interspecies differences and 10X for intra species differences. EPA has concluded that the toxicology database for clothianidin is not complete. A 10X database uncertainty factor is to be applied to all dietary exposure endpoints for the lack of a developmental immunotoxicity study.

For dietary risk assessment (other than cancer) the Agency uses the UF to calculate an acute or chronic reference dose (acute RfD or chronic RfD) where the RfD is equal to the NOAEL divided by the appropriate UF ($RfD = NOAEL/UF$). Where an additional safety factors (SF) is retained due to concerns unique to the FQPA, this additional factor is applied to the RfD by dividing the RfD by such additional factor. The acute or chronic Population Adjusted Dose (aPAD or cPAD) is a modification of the RfD to accommodate this type of FQPA SF.

For non-dietary risk assessments (other than cancer) the UF is used to determine the LOC. For example, when 100 is the appropriate UF (10X to account for interspecies differences and 10X for intraspecies differences) the LOC is 100. To estimate risk, a ratio of the NOAEL to exposures (margin of exposure (MOE) = $NOAEL/exposure$) is calculated and compared to the LOC.

A summary of the toxicological endpoints for clothianidin used for human risk assessment is shown in the following table:

Toxicological Dose and Endpoints for Clothianidin for Use in Human Risk Assessment			
Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (Females 13-50 years of age)	Developmental NOAEL = 25 UF = 1000 ^a Acute RfD = 0.025 mg/kg	FQPA SF = 1 aPAD = $\frac{\text{acute RfD}}{\text{FQPA SF}}$ = 0.025 mg/kg	Developmental rabbit study Developmental LOAEL = 75 mg/kg/day based on an increased litter incidence of a missing lobe of the lung.
Acute Dietary (General population)	NOAEL = 25 UF = 1000 ^a Acute RfD = 0.025 mg/kg	FQPA SF = 1 aPAD = $\frac{\text{acute RfD}}{\text{FQPA SF}}$ = 0.025 mg/kg	Special Neurotoxicity/Pharmacology Study in Mice and Rats LOAEL = 50 mg/kg based on transient signs of decreased spontaneous motor activity, tremors and deep respirations.

Toxicological Dose and Endpoints for Clothianidin for Use in Human Risk Assessment			
Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Chronic Dietary (All populations)	Offspring NOAEL= 9.8 UF = 1000 ^a Chronic RfD = 0.0098 mg/kg/day	FQPA SF = 1 cPAD = <u>chronic RfD</u> FQPA SF = 0.0098 mg/kg/day	2-Generation Reproduction Study Offspring LOAEL = 31.2 mg/kg/day based on decreased mean body weight gain and delayed sexual maturation, decreased absolute thymus weights in F ₁ pups and an increase in stillbirths in both generations.
Cancer (oral, dermal, inhalation)	Classification: Not Likely		

UF = uncertainty factor, FQPA SF = Special FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose

^a Additional 10x database uncertainty factor for lack of a developmental immunotoxicity study.

* The reference to the FQPA SF refers to any additional SF retained due to concerns unique to the FQPA.

Human Exposures and Risks

Acute risk

Acute dietary risk was calculated assuming that 100% of the corn and canola crops were treated and resulting crop residues are at tolerance levels. In addition, since clothianidin is a major metabolite of thiamethoxam (which has many registered uses and several pending uses), residues of clothianidin which would theoretically result from the metabolism of thiamethoxam were included in the analysis. The acute dietary exposure from food to clothianidin will occupy 7.3% of the aPAD for the U.S. population, 5.4% of the aPAD for females 13 years and older, 11% of the aPAD for all infants (less than one year old), and 16% of the aPAD for children one to two years old. In addition, there is potential for acute dietary exposure to clothianidin in drinking water. After calculating DWLOCs and comparing them to the EECs for surface and ground water, EPA does not expect the aggregate exposure to exceed 100% of the aPAD, as shown in the following table:

Aggregate Risk Assessment for Acute Exposure to Clothianidin					
Population Subgroup	aPAD (mg/kg)	% aPAD (Food)	Surface Water EEC (ppb)	Ground Water EEC (ppb)	Acute DWLOC (ppb)
General U.S. Population	0.025	7.3	3.97	1.46	810
All Infants (< 1 year old)	0.025	11	3.97	1.46	220
Children (1-2 years old)	0.025	16	3.97	1.46	210
Females (13 to 49 years old)	0.025	5.4	3.97	1.46	710
Adults (50+ years old)	0.025	6	3.97	1.46	820

Chronic risk

Chronic dietary risk was calculated assuming that 100% of the corn and canola crops were treated and resulting crop residues are at tolerance levels. In addition, since clothianidin is a major metabolite of thiamethoxam (which has many registered uses and several pending uses), residues of clothianidin which would theoretically result from the metabolism of thiamethoxam were included in the analysis. EPA has concluded that exposure to clothianidin from food will utilize 5.9% of the cPAD for the U.S. population, 9.8% of the cPAD for all infants (less than one year old) and 18% of the cPAD for children one to two years old. There are no residential uses for clothianidin that result in chronic residential exposure to clothianidin. In addition, there is potential for chronic dietary exposure to clothianidin in drinking water. After calculating DWLOCs and comparing them to the EECs for surface and ground water, EPA does not expect the aggregate exposure to exceed 100% of the cPAD, as shown in the following table:

Aggregate Risk Assessment for Chronic Exposure to Clothianidin					
Population Subgroup	aPAD (mg/kg)	% aPAD (Food)	Surface Water EEC (ppb)	Ground Water EEC (ppb)	Acute DWLOC (ppb)
General U.S. Population	0.0098	5.9	2.14	1.46	320
All Infants (< 1 year old)	0.0098	9.8	2.14	1.46	88
Children (1-2 years old)	0.0098	18	2.14	1.46	80
Females (13 to 49 years old)	0.0098	4.6	2.14	1.46	280
Adults (50+ years old)	0.0098	4.9	2.14	1.46	320

Occupational Risk

Clothianidin is intended for use as a seed treatment for corn and canola. For canola, the proposed use rate would be 150 g to 400 g a.i./100 kg seed. The application rate would be approximately 0.01 to 0.024 lb ai/acre based on a seeding rate of 6 lb. seeds/acre. For corn, the treatment rate is 0.25 or 1.25 mg ai/kernel. Based on a maximum planting rate of 35,000 seeds (kernels)/acre, the application rate would be 8.8 or 44 g ai/acre (approximately 0.02 or 0.1 lb ai/acre). Application using hopper-box, slurry-box, or similar seed treatment applications used at planting is prohibited. In addition, the proposed label specifically prohibits on-farm seed treatment, which would likely use the least efficient equipment and result in higher exposures per lb ai handled.

Chemical-specific data for assessing human exposures during pesticide handling activities were not submitted to the Agency in support of the registration of clothianidin. Instead, the registrant (Bayer) submitted surrogate studies using the chemicals Oftanol (isofenphos) and Baytan (triadimenol). Bayer Corp. also submitted two exposure assessments which used these seed treatment exposure studies as surrogates for exposure to clothianidin.

None of the baseline seed treater estimates exceed the HED level of concern (all MOEs were greater than 100). Because the Oftanol and Baytan study subjects were wearing long sleeved shirts, long pants, and chemical resistant gloves, the "baseline" risk estimates assume the same level of protection. The baseline total dermal and inhalation MOEs ranged from 380 to 960 for loader/applicators in large commercial facilities. The small/medium facility estimates reflect the addition of bagger exposure data from the Baytan study, which was from a medium sized facility. The lowest handler MOE was 110 for seed baggers in small/medium sized facilities. This exposure estimate is driven nearly equally by dermal and inhalation exposure.

The postapplication exposure scenario for seed treatment consists of the farmer purchasing bags of treated seed, placing the seed in hopper, and planting seed in fields. The MOEs for loading and planting seed were all greater than 100 (ranging from 15,000 to 26,000) and therefore, did not exceed HED's level of concern. These estimates are believed to be sufficiently conservative to be protective of all workers.

Environmental Characteristics

STUDY TYPE	HALF LIFE/OTHER
Hydrolysis	Stable
Photolysis in Water	Less than 1 day
Photolysis on Soil	34 days
Aerobic Soil Metabolism	148 to 1,155 days
Anaerobic Aquatic Metabolism	27 days
Mobility-Leaching	Mobile to highly mobile
Terrestrial Field Dissipation	277 days to 1,386 days in the 0-15 cm soil depth; generally not detected below the 45 cm soil depth

Potential to Contaminate Groundwater

Based on laboratory and field studies, the available data on clothianidin show that the compound is persistent and mobile, stable to hydrolysis, and has potential to leach to ground water and be transported via runoff to surface water bodies.

Ecological Characteristics

Terrestrial

Clothianidin is practically non-toxic to the bobwhite quail on an acute basis ($LD_{50} > 2000$ mg/kg) and practically non-toxic to the mallard duck and the bobwhite quail on a sub-acute basis (5-day $LC_{50} > 5040$ ppm and 5230 ppm, respectively). However, exposure to treated seeds through ingestion may result in chronic toxic risk to birds (exposure of 525 ppm adversely affected eggshell thickness for Bobwhite quail).

Clothianidin is moderately toxic to small mammals on an acute oral basis ($LD_{50} > 389$ mg/kg). Chronic exposure to treated seeds through ingestion may result in reproductive and/or developmental effects.

Clothianidin is highly toxic to honey bees on an acute contact basis ($LD_{50} > 0.0439$ µg/bee). It has the potential for toxic chronic exposure to honey bees, as well as other nontarget pollinators, through the translocation of clothianidin residues in nectar and pollen. In honey bees, the effects of this toxic chronic exposure may include lethal and/or sub-lethal effects in the larvae and reproductive effects in the queen.

Aquatic - Freshwater

Clothianidin is practically non-toxic to the blue-gill sunfish (96-hour LC_{50} = 117 ppm) and practically non-toxic to the rainbow trout (96-hour LC_{50} = 105 ppm). It ranges from very highly toxic to *Chironomus riparius* (48-hour EC_{50} = 0.022 ppm) to practically non-toxic to *Daphnia magna* (48-hour EC_{50} = 100.8 - 119 ppm).

Aquatic - Estuarine/Marine

Clothianidin is slightly toxic to the sheepshead minnow (96-hour LC_{50} > 93.6 ppm). It is practically non-toxic to the eastern oyster (96-hour EC_{50} = 129.1 ppm) and very highly toxic to the mysid shrimp (96-hour LC_{50} = 0.051 ppm).

Plants

Clothianidin does not appear to present a risk to terrestrial plants (seedling emergence EC_{25} > 214 ppm; vegetative vigor EC_{25} > 218 ppm). In addition, it does not appear to present a risk to aquatic vascular plants (*Lemna gibba* EC_{50} > 121 ppm) or aquatic nonvascular plants (*Selenastrum capricornutum* EC_{50} averages 70 ppm).

Endangered Species

Clothianidin is expected to present acute and/or chronic toxicity risk to endangered/threatened birds and mammals via possible ingestion of treated corn and canola seeds. Endangered/threatened non-target insects may be impacted via residue laden pollen and nectar. The potential use sites cover the entire U.S. because corn is grown in almost all U.S. states. The registrant must provide information on the proximity of Federally listed birds, mammals, and non-target insects to the proposed use sites. This information may best be provided via the FIFRA Endangered Species Task Force, but may be produced independently, providing the information is of sufficient quality to meet FIFRA and Endangered Species Act requirements. The information will be used by the EPA to develop specific recommendations to avoid adverse effects to listed species.

To address ecological concerns, labeling will be required that mandates treated seed bags be printed with advisory language regarding hazards to wildlife and will include specific instructions to cover or collect clothianidin treated seeds that are spilled during loading. In order to fully evaluate the possibility of chronic exposure to honey bees, a complete worker bee life cycle study will be required, as well as an evaluation of exposure and effects to the queen. Sediment toxicity testing will be required to address the uncertainty of possible risk to communities of invertebrates and fish that inhabit or come into contact with sediment from fields planted with treated seed.

Mechanism of Pesticidal Action

Although nicotine has been used as a pesticide for over 200 years it degraded too rapidly in the environment and lacked the selectivity to be very useful in large scale agricultural situations. However, in order to address this problem, the neonicotinoids (chloronicotinyl insecticides) were developed as a substitute of nicotine, targeting the same receptor site (AChR) and activating post-synaptic acetylcholine receptors but not inhibiting AChE. Clothianidin, like other neonicotinoids, is an agonist of acetylcholine, the neurotransmitter that stimulates the nAChR. In insects, neonicotinoids cause symptoms similar to that of nicotine. The advantage of clothianidin and other neonicotinoids over nicotine is that they are less likely to break down in the environment.

4. SUMMARY OF REGULATORY POSITION AND RATIONALE

Available data provide adequate information to support the conditional registration of Poncho 600 for seed treatment use on corn and canola.

Use, Formulation, Manufacturing Process or Geographic Restrictions

Environmental Hazards

This product is toxic to aquatic invertebrates. Clothianidin has properties and characteristics associated with chemicals detected in ground water. Contain any product spills or equipment leaks and dispose of wastes according to disposal instructions on this label. Do not contaminate water when disposing of equipment washwaters.

Use Directions - General Precautions

For use by commercial treaters only. Not for use in agricultural establishments in hopper-box, slurry-box, or similar on-farm seed treatment applicators used at planting. This product is to be used in commercial liquid or slurry treaters.

All seed treated must be conspicuously coloured at the time of treatment. An appropriate colorant must be added during application to seed to distinguish and prevent subsequent inadvertent use as a food for man or feed for animals.

Treated seed must be labeled in accordance with the requirements of the Federal Seed Act.

Required Labeling for Treated Seed Bags

Seeds are treated with clothianidin as an insecticide.

Treated seeds exposed on soil surface may be hazardous to wildlife. Cover or collect treated seeds spilled during loading.

Areas planted with treated seed may be replanted immediately with corn, rapeseed, and canola. These areas may also be replanted after 30 days with cereal grains, grasses, nongrass animal feeds, soybeans, and dried beans. Do not plant any other crop in the treated area for at least one year after treated seeds are planted.

Do not use treated seed for feed, food or oil processing.

Rapeseed greens and seed grown or harvested from treated seed must not be used for feed or human consumption.

Store away from feeds and other foodstuffs.

Wear long-sleeved shirt, long pants, and waterproof gloves when handling treated seed.

Dispose of all excess treated seed. Left over treated seed may be doublesown around the headland or buried away from water sources in accordance with local requirements. Do not contaminate water bodies when disposing of planting equipment washwaters.

Dispose of seed packaging in accordance with local requirements.

5. **SUMMARY OF DATA GAPS**

Toxicology:

- Developmental immunotoxicity study
- Additional analysis of test materials used in mutagenicity studies

Residue Chemistry:

- Rotational crop residue field trials with mature soybeans

Environmental Fate Data:

- Aerobic aquatic metabolism
- Seed leaching study

Ecological Effects Data:

- Whole sediment acute toxicity to freshwater invertebrates
- Field test for pollinators

6. **CONTACT PERSON AT EPA**

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DISCLAIMER: The information presented in this Pesticide Fact Sheet is for informational purposes only and may not be used to fulfill data requirements for pesticide registration and reregistration.

INFORME DE BÚSQUEDA DE PATENTES PARA EL No de Radicación: 14- 121257						
CRITERIOS PARA LA BÚSQUEDA (anexar pantallazo o reporte en PDF, junto con los boleanos utilizados)						
Palabras clave utilizadas		-Acaricides -Clothianidin -Triazole - Triazolylphenyl sulfide				
CLASIFICACIONES INTERNACIONALES UTILIZADAS PARA LA BÚSQUEDA		A01P 7/00; A01N 43/653, 63/00, 63/04, 43/90, 47/40, 53/00, 43/88, 43/56, 43/36, 57/16, 51/00, 47/34, 57/12 y 47/02				
BASES DE DATOS CONSULTADAS.						
Spacenet						
Google patents						
INFORMES DE EXÁMENES REALIZADOS EN OTRAS OFICINAS (documentos patentes, literatura no patente etc...)						
Oficina	Fecha del examen o de reporte de búsqueda de documentos	Anterioridades encontradas para el examen o reportados en el examen de búsqueda(relacionarlos todos)	Reiv. afectadas	RELEVANCIA (requisito que afecta)	FUERON TENIDOS EN CUENTA PARA EL EXAMEN EN LA OFICINA COLOMBIANA	
					SI	NO
EUROPEA	11/03/2013	EP2382865	1-5, 13	Nivel Inventivo		X
		WO2011152320	1-13	Nivel Inventivo		X
		WO2011020567	1-5,13	Nivel Inventivo		X
		WO2011029506	1-5,13	Nivel Inventivo		X
DOCUMENTOS ADICIONALES ENCONTRADOS POR EL EXAMINADOR DE ACUERDO A LOS CRITERIOS DE BÚSQUEDA.						
Clothianidin						
Pesticide Fact Sheet Clothianidin						
BÚSQUEDA DE SECUENCIAS						
Número de depósito / patente y N° de secuencia % de identidad						
SEQ ID NO (de la solicitud)	NCBI	The Lens	EMBL-EBI	DDJB	Genome Quest	
	No aplica					

CRITERIOS DE BÚSQUEDA / UNIDAD DE INVENCION (Pantallazos)