

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO	
RAD: 14-274207- -1	FECHA: 2015-05-18 17:01:36
DEP: 2020 DIRECCION DE NUEVAS CREACIONES	EVE: 378 FASE NACIONAL INCLUIDO CAPITULO I
TRA: 11 PCT-PATENTE DE INVENCION CAPITULOS I Y II	FOLIOS: 15
ACT: 519 TRASLADOINFORME	

DIRECCIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado(a)/Señor(a)
JAIME EDUARDO DELGADO VILLEGAS

Asunto: Radicación: 14-274207- -1
 Trámite: 11
 Evento: 378
 Actuación: 519
 Oficio: 5430
 Folios: 15

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/EP2011/071418				
Fecha de Presentación Internacional	30/11/2011				

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 14-274207-00000-0000	12/Diciembre/2014
Reivindicaciones:	Radicado 14-274207-00000-0000	12/Diciembre/2014
Prioridad:	EP 10193335.6	01/Diciembre/2010
	US 61/419,438	03/Diciembre/2010

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. Presentación de solicitudes Fraccionarias (Art 36 D 486)

La presente solicitud corresponde a una divisional de la solicitud parental 13-133020-00000-0000.

4. 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 estudiarán las reivindicaciones 1 a 12 de acuerdo con el radicado 14-274207-00000-0000.

Título de la solicitud: "Combinaciones de principios activos que comprenden piridietilbenzamidas y otros principios activos".

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

Para resolver este problema técnico la solicitud en estudio proporciona una combinación de fluoripam y piretrum.

El objeto de la presente solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): A01N31/08, 43/28, 57/32; A01P5/00, 7/04.

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 familia química o su actividad biológica, por lo anterior, se sugiere restringir el título incluyendo las características técnicas inventivas. Además, es necesario que el título permita distinguir la presente solicitud de la solicitud original y sus divisionales.

Reivindicaciones (Art 30 D 486, Art 22 PCT)

La reivindicación 1 se encabeza como una combinación entre los compuestos fluopiram y piretrum, sin embargo, de acuerdo con los ejemplos sustentados lo definido corresponde a composiciones, por lo que, se sugiere cambiar el encabezado combinación por composición. Además, las reivindicaciones deben ser claras en cuanto al tipo producto que reclaman.

La reivindicación 1 no es clara porque hace referencia a piretrum, sin definir el ingrediente activo como tal. Se sugiere realizar la aclaración necesaria.

La reivindicación 2 no es clara porque reclama una procedimiento de preparación sin definirlo en términos de una serie lógica y ordenada de etapas, además, no establece en estas las condiciones, ingredientes y parámetros que permiten alcanzar el objeto propuesto. Se sugiere hacer las aclaraciones necesarias.

La reivindicación 3 no es clara porque define los excipientes en términos de su función dentro de la composición, se recuerda, que los excipientes se deben definir en términos de su nombre común y proporciones dentro de la composición, se sugiere hacer las aclaraciones necesarias.

Las Reivindicaciones 2-3 incluyen las expresiones “composiciones insecticidas y/o acaricidas y/o nematocidas” y “combatir plagas animales” que refieren el uso de la composición reivindicada, el cual no es una característica técnica que defina a la invención. Se sugiere eliminar dichas expresiones.

La reivindicación 4 no es clara porque la expresión “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 10 no es clara porque reclama la inclusión de arcillas modificadas sin caracterizarlas, se sugiere hacer las precisiones necesarias.

Las reivindicaciones 2-12 no son concisas porque las definiciones de los excipientes son generales, por lo que se sugiere restringir la solicitud a una razonable generalización de los excipientes probados, es decir, que se encuentran debidamente sustentados a través de ejemplos concretos de acuerdo con lo presentado en la tabla No 1.

Tabla No. 1 Excipientes de las composiciones soportadas.

Excipientes	Ejemplos probados
Tensioactivos	No sustenta
Diluyentes	No sustenta
Disolventes	Acetona, dimetilformamida
Colorantes	No sustenta
Humectantes	No sustenta
Dispersantes y/o emulsionantes	No define (alquilarilpoliglicoléter)
Antiespumante	No sustenta
Conservante	No sustenta
Espesante	No sustenta
Adhesivos	No sustenta
Gibelinas	No sustenta

Las reivindicaciones 2-12 reclaman que la composición incluye tensioactivos, diluyentes, colorantes, humectantes, antiespumantes, conservantes, espesantes, adhesivos y gibelinas, sin embargo, dentro del capítulo descriptivo no se definen ejemplos concretos de composiciones que comprendan los mencionados excipientes, se aclara, que la mera mención de la posibilidad de incluir unos excipientes seleccionados de una extensa lista no es suficiente soporte, las composiciones se deben definir en términos de sus ingredientes (DCI/IUPAc para

los activos y nombre común para los excipientes) y proporciones, por lo anterior, se sugiere eliminar de las mencionadas cláusulas los excipientes no sustentados.

Se requiere al solicitante hacer las aclaraciones necesarias.

6. 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 01 de 2010. 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	US20100249193	"Nematicidal, Insecticidal and Acaricidal Active Ingredient Combinations Comprising Pyridylethylbenzamides and Insecticides"	30/Septiembre/2010
D2	WO2006107905	"Stable pesticide concentrates and end-use emulsions"	12/Octubre/2006

El documento D1⁽¹⁾ divulga combinaciones que comprenden fluopiram útiles en el control de plagas producidas por insectos, ácaros y nematodos en suelo, hojas y semillas (Resumen y Pág. 11, Rv. 1).

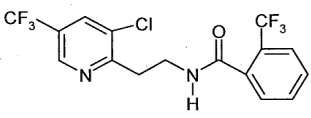
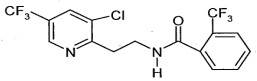
El documento D2⁽²⁾ divulga composiciones pesticidas que comprenden combinaciones de compuestos fungicidas y piretrum para el control de plagas (Resumen y Pág. 24, Rvs. 1-2).

7. Examen de Patentabilidad (Art 14 D486)

Nivel inventivo (Art18 D486)

La reivindicación 1 consiste en "La reivindicación 1 consiste en la *Combinaciones de principios activos que comprenden fluopiram y piretrum*".

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

Características esenciales	D1	D2
Combinación que comprenden:	Combinación de ingredientes que comprende: (Pág. 11, Rv. 1)	Pesticida que comprende: (Pág. 24, Rvs. 1-2)
 (Fluopiram)	 (Fluopiram) (Pág. 11, Rv. 1)	Fungicida (Pág. 24, Rvs. 1-2)
Piretrum	No menciona	Piretrum

1. [www.espacenet/ US20100249193](http://www.espacenet/US20100249193)

2. [www.espacenet/ WO2006107905](http://www.espacenet/WO2006107905)

		(Pág. 24, Rvs. 1-2)
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Los documentos D1 y D2 se consideran el estado de la técnica cercano a la invención definida en la reivindicación 1 porque en el caso del documento D1 divulga combinaciones que comprenden fluopiram útiles en el control de plagas producidas por insectos, ácaros y nematodos en suelo, hojas y semillas (Resumen y Pág. 11, Rv. 1). Por su parte, el documento D2 divulga composiciones pesticidas que comprenden combinaciones de compuestos fungicidas y piretrum para el control de plagas (Resumen y Pág. 24, Rvs. 1-2).

La diferencia entre la combinación, definida en la reivindicación 1 y la combinación revelada en el documento D1 consiste en que la combinación reclamada incluye piretrum, mientras que la combinación divulgada en el documento D1 no incluye piretrum.

El efecto que logra el utilizar al piretrum en la combinación consiste en que se aumenta la capacidad de combate de ésta contra las plagas.

Por lo tanto, el problema técnico objetivo que pretende resolver esta invención se puede formular así: “cómo proporcionar combinaciones que comprendan Fluopiram útiles para el control de las infestaciones de plagas”.

Sin embargo, la combinación de un agente químico fungicida con piretrum útil para tratar infestaciones de plagas en plantas, está divulgada en el documento D2 que enseña composiciones pesticidas que comprenden combinaciones de compuestos fungicidas y piretrum para el control de plagas (Resumen y Pág. 24, Rvs. 1-2).

Además, es parte del conocimiento de la persona normalmente versada en la materia que el piretrum corresponde a compuestos insecticidas naturales derivados de las flores del crisantemo que actúan sobre los nervios del insecto causándole parálisis, de acuerdo con lo divulgado en el documento “PYRETHRINS/PYRETHRUM”⁽³⁾.

En consecuencia, la persona del oficio normalmente versada en la materia, incluiría dentro de la combinación divulgada en el documento D1 al piretrum de acuerdo con lo revelado en el documento D2, para llegar así al objeto de la reivindicación 1 de la solicitud. Por lo cual se considera obvia.

Puesto que las reivindicaciones dependientes 2-12 no mencionan características técnicas esenciales acerca de la combinación, tampoco se pueden considerar inventivas.

8. Conclusión

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

Ítem	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	US20100249193	1-12	Nivel inventivo
D2	WO2006107905	1-12	Nivel inventivo

3 . <http://www.pesticide.org/get-the-facts/pesticide-factsheets/factsheets/pyrethrinspyrethrum>

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 2015-05-26

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

INFORME DE BÚSQUEDA DE PATENTES PARA EL No de Radicación: 14-274207						
CRITERIOS PARA LA BÚSQUEDA (anexar pantallazo o reporte en PDF, junto con los boleanos utilizados)						
Palabras clave utilizadas		-Piretro -Crisantemo -piretrum -pyrethrum natural insecticide -pyrethrum insecticide combination -combined pyrethrum insecticide and fungicide -synergym pyrethrum insecticide and fungicide -pyrethrum and fungicide and compositions				
CLASIFICACIONES INTERNACIONALES UTILIZADAS PARA LA BÚSQUEDA		A01N31/08, 43/28, 57/32; A01P5/00, 7/04				
BASES DE DATOS CONSULTADAS.						
Google Patents						
WIPO						
Spacenet						
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	01/06/2013	WO2010108616	1-10	Novedad y Nivel Inventivo	X	
DOCUMENTOS ADICIONALES ENCONTRADOS POR EL EXAMINADOR DE ACUERDO A LOS CRITERIOS DE BÚSQUEDA.						
Environmental Fate of Pyrethrins						
Pyrethrin						
PYRETHRINS/PYRETHRUM						
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 INVENCIÓN (Pantallazos)

No aplica

● INSECTICIDE FACTSHEET

PYRETHRINS/PYRETHRUM

Pyrethrins and pyrethrum are the most frequently used home and garden insecticides in the U.S. They are often used in indoor sprays, pet shampoos, and aerosol bombs to kill flying and jumping insects.

Pyrethrins are a common cause of insecticide poisonings. According to a U.S. Environmental Protection Agency (EPA) survey of poison control centers, they cause more insecticide poisoning incidents than any other class of insecticides except the organophosphates. Symptoms include headaches, dizziness, and difficulty breathing.

Pyrethrins can trigger life-threatening allergic responses including heart failure and severe asthma.

In laboratory animals exposed through eating, by injection, or through breathing, pyrethrins have caused anemia.

Experiments with dairy cows suggest that nursing mothers exposed to pyrethrins can pass them on to their children.

Pyrethrins disrupt the normal functioning of sex hormones. They inhibit binding of sex hormones to human genital skin and proteins in human blood.

Pyrethrins are classified as "likely to be human carcinogens" by EPA because they cause thyroid tumors in laboratory tests. Farmers who use pyrethrins have an increased risk of developing leukemia.

Pyrethrins are extremely toxic to bees, fish, and other aquatic animals.

Following indoor treatments, pyrethrins have persisted up to 2 1/2 months in carpet dust.

BY CAROLINE COX

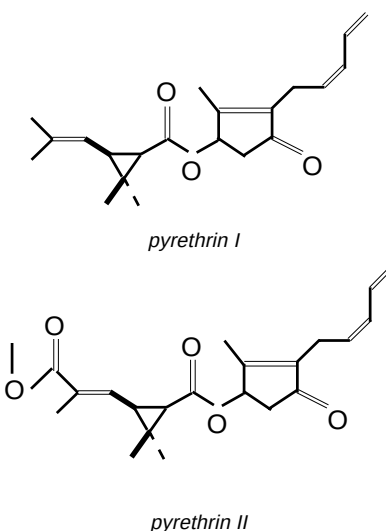
Pyrethrum and pyrethrins have been used as insecticides since at least 1800¹ and for decades have been the most commonly used home and garden insecticides in the U.S.^{2,3} Pyrethrum is a natural insecticide, an extract made from two daisy-like flowers, *Chrysanthemum cinerariaefolium* and *Chrysanthemum cinereum*. Pyrethrins are the six insecticidally active compounds in pyrethrum.¹ (See Figure 1 for two examples.) Pyrethrins are mainly used as indoor sprays, pet shampoos, and aerosol bombs to kill flying and jumping insects.¹ Although pyrethrins are natural insecticides, they do pose important hazards to human and environmental health. This article summarizes those hazards.

Pyrethrin insecticides often contain piperonyl butoxide, a chemical that increases the potency of pyrethrins.⁴



Caroline Cox is NCAP's staff scientist.

Figure 1
Two of the Pyrethrin Esters



The health and environmental hazards of piperonyl butoxide will be summarized in the summer 2002 issue of the *Journal of Pesticide Reform*.

A large family of insecticides, the synthetic pyrethroids, are structurally similar to pyrethrins but have been chemically modified to make them more toxic and more persistent.¹ For information about the hazards of three commonly used synthetic pyrethroids see JPR 14(2): 28-34 (cyfluthrin); JPR 16(2): 15-20 (cypermethrin); and JPR 18(2): 14-20 (permethrin).

Use

In the early part of the twentieth century pyrethrum was "the most commonly used household insecticide."² The most recent U.S. Environmental Protection Agency (EPA) home and garden pesticide survey estimated that over 240 million of these applications are made annually in the U.S., more than any other insecticide.³ There are more registered uses for pyrethrins than for any other insecticide.⁵ Worldwide, about 200,000 kilograms (440,000 pounds) of pyrethrins are used each year.⁶

Other than home and garden uses, pyrethrins are used on a variety of

agricultural crops and for structural and public health pest control. The amount used in agriculture is small relative to the other uses.⁷ (See Figure 2.)

Mode of Action

Pyrethrins, like all members of the pyrethroid insecticide family, kill insects by disrupting their nervous systems. Pyrethrins are toxic to the “sodium channel,” the cellular structure that allows sodium ions to enter a cell as part of the process of transmitting a nerve impulse. This leads to repetitive discharges by the nerve cell which causes paralysis and death.⁸ DDT and related insecticides have the same mode of action.⁹

Nerves in humans and other mammals are also susceptible to pyrethrin poisoning. However, mammals have enzymes that more rapidly detoxify pyrethrins into compounds that don't disrupt the nervous system.¹⁰

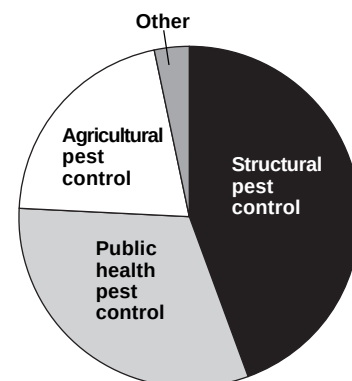
Inert Ingredients

Like most pesticides, commercial pyrethrin-containing insecticides contain ingredients other than pyrethrins which, according to U.S. pesticide law, are called “inert.”¹¹ Except for acute toxicity testing, all toxicology tests required for registration of pyrethrin products were conducted with pyrethrins, not with the combination of ingredients found in commercial products.¹² Most inert ingredients are not identified on product labels, and little information about them is publicly available. For more information about the hazards of some of the inert ingredients in pyrethrin products see “Hazards of Inert Ingredients,” below.

Acute poisoning

Frequency: Pyrethrins are a common cause of insecticide poisonings. When EPA summarized calls to poison control centers in 1991, the agency found that pyrethrins, and pyrethrins

Figure 2
Pyrethrin Use in California



Note: This chart does not include household use.

Source: Calif. EPA. Dept. of Pesticide Regulation. 2001. Summary of pesticide use report data: 2000, indexed by chemical. Pp. 341-343. www.cdpr.ca.gov.

California data suggest that agricultural uses of pyrethrin are small relative to other uses.

HAZARDS OF INERT INGREDIENTS

Propane is used as an inert propellant in pyrethrin products. (See footnote 1 for some examples.) It can cause dizziness when inhaled. It is also “extremely flammable”² and easily ignited by heat, sparks, or flame.²

Isobutane is also used as an inert propellant in pyrethrin products. (See footnote 3 for some examples.) It depresses the central nervous system and can cause dizziness when inhaled. Like propane, it is “extremely flammable”⁴ and easily ignited.⁴

Hydrotreated light petroleum distillates (hydrotreated kerosene) are used as an inert solvent in pyrethrin products. (See footnote 5 for some examples.) The Chemical Abstract Services number for this solvent is 64742-47-8. This solvent has caused skin tumors when applied to the skin of laboratory mice.⁶

Hydrotreated heavy naptha (white spirits) is also used as an inert solvent in pyrethrin products. (See footnote 7 for some examples.) The Chemical Abstract Services number for this solvent is 64742-48-9. It is damaging to kidneys and the nervous system.⁸ In a recent laboratory study, the offspring of animals exposed to white spirits developed “long-lasting and possibly irreversible changes” in brain cells. This damage to the brain was caused by an inability to maintain normal calcium concentrations.⁹

1. Whitmire Micro-Gen. 1998. MSDS: P.I. Contact Insecticide. www.wmmg.com/pest/products/pdf/MSDS/pi.pdf; Value Garden Supply. Undated. MSDS: Black Leaf Home Insect Fogger. www.valuegardens.com/msds/Home%20Insect%20Fogger.pdf; Amrep, Inc. 1997. MSDS: Misty Fog Plus Fogger. www.amrep.com/ii/products/msds/aerosols/476.pdf.
2. Hazardous Substance Data Bank. 2001. Propane. <http://toxnet.nlm.nih.gov>.
3. Value Garden Supply. Undated. MSDS: Black Leaf Home Insect Fogger. www.valuegardens.com/msds/Home%20Insect%20Fogger.pdf; Amrep, Inc. 1997. MSDS: Misty Fog Plus Fogger. www.amrep.com/ii/products/msds/aerosols/476.pdf.
4. Hazardous Substance Data Bank. 2001. Isobutane. <http://toxnet.nlm.nih.gov>.
5. Cardinal Chemical Company. Undated. MSDS: Py-Dry. www.cardinalproducts.com/MSDS/PY-Dry%20msds%202.pdf; Aventis. 2001. MSDS: Pyrenone 25-5 Public Health. www.adapcoinc.com/pdf/PYR25m.pdf; Southern Agricultural Insecticides, Inc. 1997. MSDS: Natural Pyrethrin Concentrate. www.southernag.com/ms1040.pdf; Waterbury Co., Inc. 2001. MSDS: Pro Exterminator Crawling & Flying Insect Killer. www.timemist.com/proexterminator/msds/ProExtCrawlingFlying.pdf; Waterbury Companies, Inc. 2001. MSDS: Country Vet Farm & Home CV-38 for Insect Control. www.country-vet.com/products/347300CV.pdf.
6. International Agency for Research on Cancer. 1989. Occupational exposures in petroleum refining. *IARC Monographs* 45:39. <http://193.51.164.11/htdocs/monographs/Vol45/45-01.htm>.
7. Whitmire Micro-Gen. 1998. MSDS: P.I. Contact Insecticide. www.wmmg.com/pest/products/pdf/MSDS/pi.pdf.
8. United Nations Environment Prog. et al. 1996. White spirit (Stoddard Solvent). *Environmental Health Criteria* 187. Geneva, Switzerland: World Health Organization. Pp.73-75, 77-78, 90-128.
9. Edelfors, S., U. Hass, and A. Ravn-Jonsen. 1999. The effect of in vitro exposure to white spirit on $[Ca^{2+}]$ in synaptosomes from rats exposed prenatally to white spirit. *Pharmacol. Toxicol.* 84: 197-200.

with the synergist piperonyl butoxide, caused over 9,000 incidents. Only the organophosphate insecticides caused more insecticide poisoning incidents.¹³ (See Figure 3.)

Symptoms: Some symptoms of pyrethrin poisoning in people, headaches and dizziness, are related to disruptions of the nervous system. For example, the Centers for Disease Control compiled reports of pyrethrin exposure incidents including one in which a cook developed these symptoms following installation of pyrethrin insecticide dispensers in the restaurant where he worked. A customer in the same restaurant developed similar symptoms.¹⁴

The patients also developed other symptoms that may not be related directly to pyrethrins' effect on the nervous system: sore throat and difficulty breathing.¹⁴

Physiological mechanisms: Laboratory tests have demonstrated that pyrethrins cause several neurological disruptions in mammals. These may be the cause of the sodium channel

disruption that results in their toxic effects in insects, or an additional effect. (See "Mode of Action," p. 15.) For example, researchers from the University of Maryland School of Medicine and the University of Alexandria (Egypt) showed that pyrethrins inhibited calcium uptake in rat brain cells. Calcium plays a "vital role"¹⁵ in the nervous system, promoting the normal release of transmitter chemicals from junctions between nerves and stabilizing the membrane surrounding nerve cells.¹⁵ Two groups of researchers, from the University of Mississippi Medical Center¹⁶ and the University of Tampere Medical School (Finland)¹⁷ showed that pyrethrins disrupt energy production in brain cells.

Pyrethrins also affect physiological processes that are not related to the nervous system. For example, researchers at the Osaka City Institute of Public Health and Environmental Sciences (Japan) showed that in rat livers pyrethrins inhibit mitochondria, the cellular bodies that convert food to usable energy.¹⁸

Allergic Responses to Pyrethrins

Pyrethrins can trigger allergic responses that range from unpleasant to life-threatening. Skin rashes, asthma, and hives caused by exposure to pyrethrins or pyrethrum have been reported in medical literature since the 1920s and 1930s.¹⁹

More serious reports were published in 1994 and 2000. Physicians in New York reported that a woman developed shortness of breath five minutes after beginning to wash her family dog with a pyrethrin shampoo. Almost immediately she suffered heart failure and died after paramedics transported her to a hospital.²⁰ An Oregon physician reported that an 11-year-old girl developed a severe asthmatic attack when washing the family dog with a pyrethrin shampoo. She died a few hours later, despite medical treatment.²¹

The refined pyrethrins in the products that caused these incidents are less allergenic than unrefined pyrethrum²² but still have caused these serious reactions.

Eye irritation

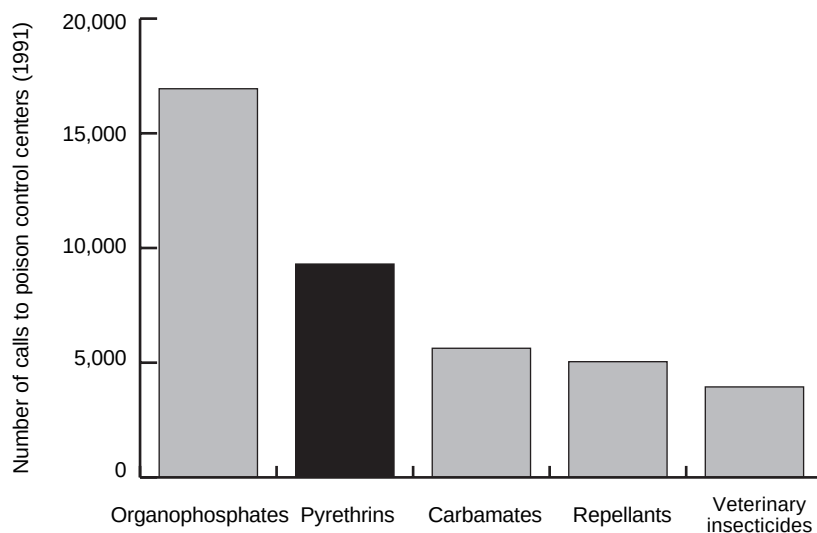
People exposed to commercial pyrethrin products have reported swelling, redness, and burning of the eyes following exposure.¹⁴

Effects on the Circulatory System

Pyrethrins affect both sugar levels and oxygen-carrying ability of blood. Researchers from the University in Rajasthan (India) showed that an injection of pyrethrins caused gerbil blood sugar levels to rise between 30 and 70 percent (depending on dose). Blood sugar peaked an hour after treatment, but the increase persisted for several days.²³ The same researchers showed that an injection of pyrethrins caused a decrease in the amount of hemoglobin (oxygen-carrying molecules) in the blood,²⁴ as well as a decrease in the number of red blood cells.²⁵ Hemoglobin concentration remained low for 2–3 weeks (see Figure 4);²⁴ the reduced number of red blood cells persisted for 2 days.²⁵

Other types of exposures with a

Figure 3
Frequency of Pyrethrin Poisonings



Sources: U.S. EPA. Office of Pesticides and Toxic Substances. Undated memo. Human insecticide exposures reported to Poison Control Centers in 1991. Prepared by J. Blondell, Health Effects Division.

Pyrethrin poisonings are more frequent than poisoning cause by any other class of insecticide except the organophosphates.

longer duration caused similar effects. A three-month feeding study with rats found pyrethrins caused a decrease in the amount of hemoglobin in females at doses at or above 170 milligrams of pyrethrins per kilogram of body weight (mg/kg) per day (the middle dose in this experiment). Similar effects were found in males at higher exposures. A three month inhalation study found that pyrethrins caused anemia at doses at or above 0.07 milligrams per liter of air in males (all but the lowest dose in this experiment). They also caused anemia in females, although at higher exposures.²⁶

Effects on the Kidney

A three-month feeding study with rats showed that pyrethrins caused degeneration of tubules (small tube-like structures) in the kidney at doses equal or greater than 170 mg/kg.²⁷

Effects on Reproduction

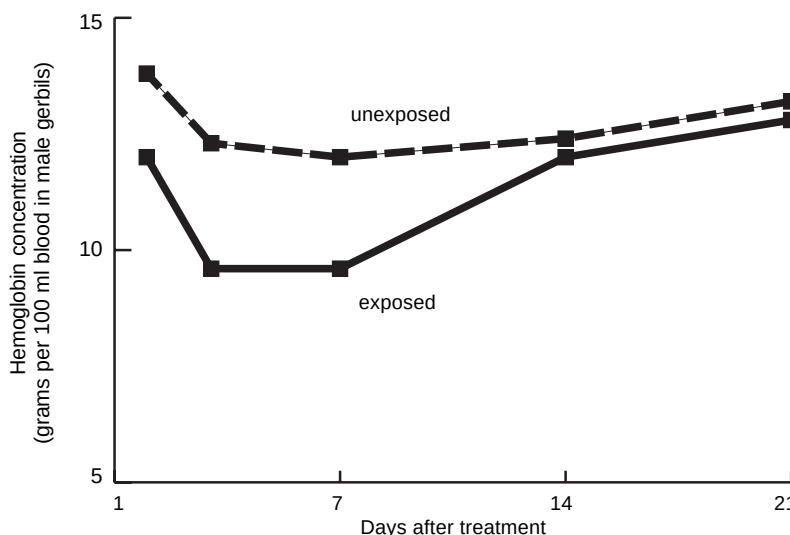
Pyrethrins can disrupt successful reproduction in both males and females. In a two-month feeding study with dogs, the weight of the testes in animals exposed to pyrethrins at doses at or above 30 mg/kg (all but the lowest dose tested) was less than that of unexposed animals.²⁸ In a two-generation feeding study with rats, the weight of offspring at birth and during nursing was less for rats fed pyrethrins at doses at or above 65 mg/kg (all but the lowest dose tested) than for unexposed animals.²⁹

Concerns about pyrethrins' effects on reproduction are heightened by studies of dairy cows. Following treatment of the cows with pyrethrins, pyrethrins were detected in the cows' milk.³⁰ This study provides support for the concern that exposed nursing mothers could pass pyrethrins on to their children.

Disruption of Hormone Systems

The impact that environmental pollutants can have on the normal function of human and animal hormone systems has been a significant concern in the last decade.³¹ Hormones are biologically active molecules that control all responses and functions of

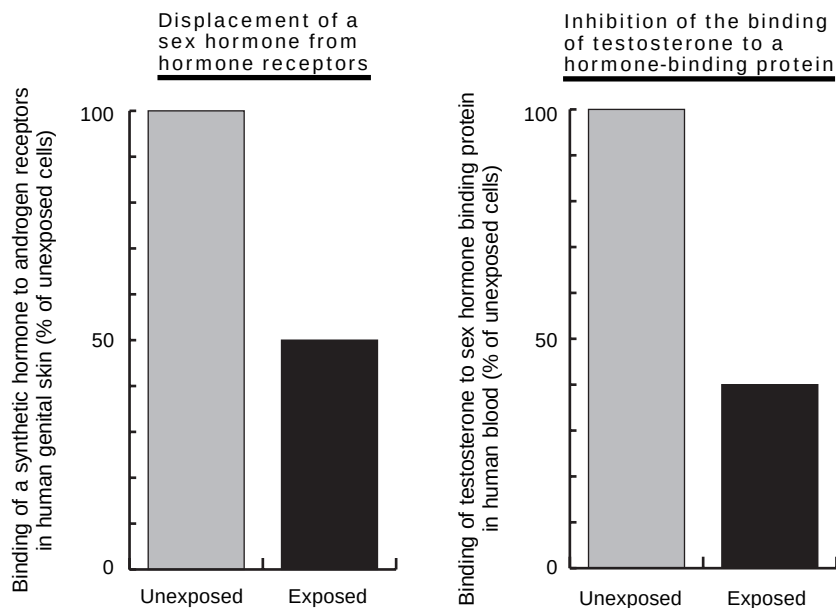
Figure 4
Exposure to Pyrethrins Causes Anemia



Source: Saxena, S.C. and A.K. Karel, 1974. A note on the effect of pyrethrum on haemoglobin concentration of Indian desert gerbils, *Meriones hurrianae*. *Pyreth. Post* 12:161-162.

A single dose of pyrethrins (by injection) caused anemia which persisted for two weeks.

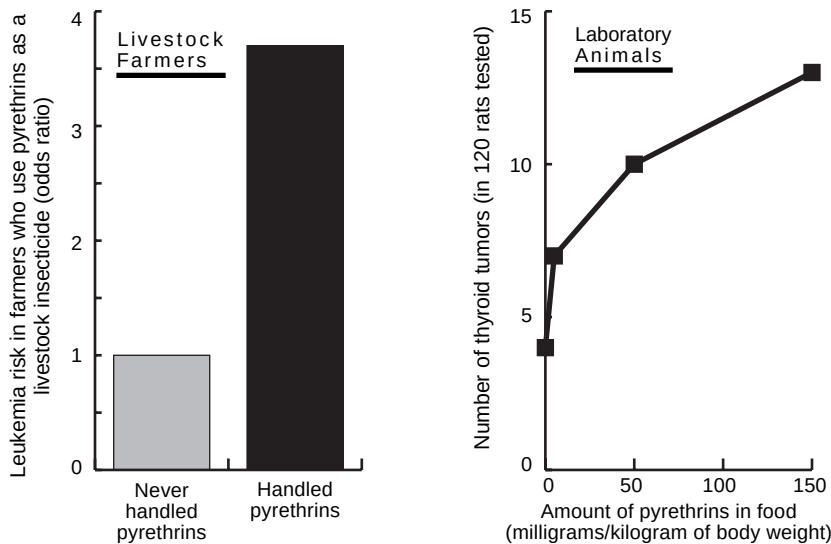
Figure 5
Exposure to Pyrethrins Disrupts Normal Hormone Functions



Source: Eil, C. and B.C. Nisula, 1990. The binding properties of pyrethroids to human skin fibroblast androgen receptors and to sex hormone binding globulin. *J. Steroid Biochem.* 35: 409-414.

In experiments with human cells, pyrethrins inhibited the normal binding of sex hormones.

Figure 6
Exposure to Pyrethrins is Associated with Increased Cancer Risks in Farmers and Laboratory Animals



Sources:

Brown, L.M. et al. 1990. Pesticide exposures and other agricultural risk factors for leukemia among men in Iowa and Minnesota. *Cancer Res.* 50: 6585-6591.
World Health Organization and Food and Agricultural Organization. 2000. Pesticide residues in food — 1999. [Part II] Toxicological evaluations. Geneva, Switzerland: World Health Organization. p. 281.

Pyrethrins are associated with an increased leukemia risk in farmers who use them to control livestock pests. They also cause an increased frequency of thyroid tumors in laboratory studies.

the body. Dramatic changes in the activity of cells in humans and other animals “are caused by extremely small amounts” of hormones or other chemicals that disrupt this system.³²

Pyrethrins appear to disrupt the normal functioning of sex hormones. Researchers from Brown University and the National Institutes of Health showed that pyrethrins displace hormones from androgen receptors in cell cultures of human genital skin. Androgens are sex hormones that promote development of male sex characteristics; testosterone is a familiar example. The same researchers also showed that pyrethrins block the binding of testosterone to the sex hormone binding protein in human blood. In both experiments pyrethrins were more potent than the synthetic pyrethroids tested.³³ (See Figure 5.)

Pyrethrins also inhibit binding to peripheral benzodiazepine receptors, found in high concentration in the testes and thought to be involved in “ste-

roid metabolism or hormonal responsiveness.” As in the study summarized in the previous paragraph, in this experiment pyrethrins were more potent than the synthetic pyrethroids tested.³⁴

Carcinogenicity

Pyrethrins are associated with increased cancer risks among farmers and have also caused cancer in laboratory tests. (See Figure 6.)

Researchers from the National Cancer Institute studying risk factors for leukemia found that farmers exposed to pyrethrins used for pest control on livestock had an increased risk of developing leukemia. Exposure to pyrethrins was associated with a 3.7-fold increase in risk.³⁵

In 1999, EPA evaluated the ability of pyrethrins to cause cancer. The agency concluded that pyrethrins should be classified as “likely to be a human carcinogen by the oral route.” This EPA evaluation was based on tests which demonstrated increases in the

frequency of several cancers in rats. The incidence of liver tumors was higher in exposed female rats than in unexposed ones. Also, in both sexes, the incidence of thyroid tumors was greater in exposed rats than in unexposed ones.³⁶

Other carcinogenicity studies showed that the incidence of lung cancers in exposed male mice was greater than in unexposed ones³⁷ and that the incidence of parathyroid tumors was greater in exposed rats than in unexposed ones.³⁸

Effect of Gender

Several laboratory studies suggest that females may be more susceptible to pyrethrins than males. The distribution of pyrethrins in rats after exposure is highest in body fat. However, the concentration in female fat was approximately double that found in male fat. Also, the median oral lethal dose for male rats was over twice the dose required to kill females.³⁹

Human Exposure

Pyrethrins are absorbed slowly through the stomach, intestines, and skin. However, pyrethrins can be absorbed “more quickly through the lungs.”⁴⁰ This suggests that exposure through breathing droplets or airborne particles deserves particular attention.

Synergy

Carboxyesterases, enzymes that detoxify pyrethrins, are inhibited by organophosphate insecticides, thus organophosphate insecticides increase pyrethrins’ toxicity.¹⁰

Effects on Cats

Cats are particularly susceptible to pyrethrin poisoning because their livers inefficiently detoxify this insecticide.⁴¹ As a consequence, there are a large number of poisoning incidents. Veterinarians summarizing calls made to an animal poison control center in 1986 found that pyrethrin-related incidents were more numerous than incidents involving any other insecticide.⁴²

Symptoms of pyrethrin poisoning in cats include excessive salivation, altered behavior, depression, anorexia, and high body temperature.⁴²

Young cats (less than four years old, but especially if less than one year old) are more susceptible to pyrethrins than older cats.⁴¹

Effects on Birds

In general, relatively large amounts of pyrethrins are required to kill birds.⁴³ However effects other than death have been found at lower exposures. Scientists from the University of Rajasthan (India) found that doses between 10 and 50 mg/kg of pyrethrum caused excitability and decreased appetites in pigeons.⁴⁴ In sparrows, doses of 400 mg/kg caused excitability and an increase in flying, as well as a decrease in food consumption and weight. The weight of the liver, intestine, pancreas, kidney, and testes also decreased.⁴⁵

Effects on Fish

Pyrethrins are "extremely toxic to fish," according to the Agency for Toxic Substances and Disease Registry.⁴⁶ Median lethal concentrations (the concentration that kills half of a test population) range from 9 to 58 parts per billion. A summary by the U.S. Fish and Wildlife Service found that channel catfish and coho salmon were the most susceptible species.⁴⁷

Pyrethrins are more toxic to fish in warm water than in cold water.⁴⁷

Effects on Other Aquatic Animals

Aquatic animals other than fish are also killed by low concentrations of pyrethrins. The most susceptible larval stage of the American lobster is killed by concentrations of 1 part per billion.⁴⁸ The scud (a fresh water crustacean) is killed by concentrations of 12 parts per billion.⁴⁹

Effects on Honey Bees

Pyrethrins are "highly toxic" to bees; 0.02 micrograms is sufficient to kill a bee.⁵⁰ Toxicity of commercial pyrethrin products to bees was demonstrated by an entomologist at Auburn University who showed that a commercial pyrethrin insecticide caused 100 percent "knockdown," the inability of the bee to walk or fly. Some of the inert ingredients used in pyrethrin products

appear to increase knockdown potency.⁵¹

Effects on Other Beneficial Insects and Spiders

It is not surprising that pyrethrins, because they are insecticides, are toxic to agriculturally useful insects and spiders. The International Organization for Biological Control found that a commercial pyrethrin product killed over 99 percent of two parasitoid wasps and a predatory fly. (Parasitoids are insects which develop in and kill the eggs or larvae of another species.) This study also found pyrethrins caused 80 percent mortality of two other parasitoid species, a fly and a wasp.⁵² Cornell University Agricultural Experiment Station researchers found that pyrethrins killed four common species of wasp that are parasitoids of house and stable flies in dairies.⁵³ The web-building spider *Argiope argentata* is also susceptible to pyrethrins; two commercial pyrethrin products caused more than 50 percent mortality of this spider in a test conducted at the University of Regensburg (Germany).⁵⁴

Development of Resistance in Pest Insects

At least fifteen species of insects, including lice, cockroaches, weevils, bedbugs, house flies, mosquitos, meal moths, and aphids have developed pyrethrin resistance, the ability to survive treatment. Resistance ratios (the ratio between the amount needed to kill a resistant individual and the amount needed to kill a susceptible individual) are often relatively low, but in four species resistance ratios are above 100. The four species are the German cockroach, the granary weevil, and two house flies.⁵⁵

Repeated exposure to synthetic pyrethroids can cause the development of resistance to pyrethrins.⁵⁵

Persistence

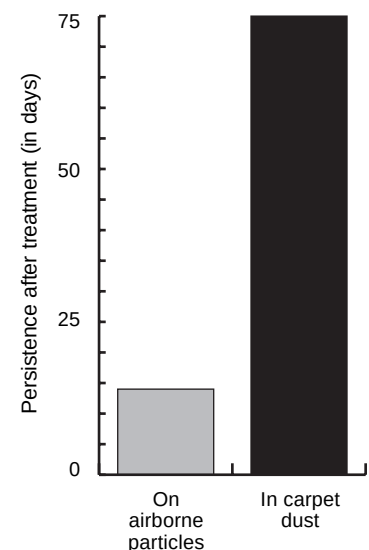
Outdoors, pyrethrins persist only for a short time. For example, after application of pyrethrins to bare soil, the half life (the time required for half of the applied pyrethrin to break down or move away from the application site) was two hours or less.⁵⁶

Pyrethrins persist much longer indoors than they do outdoors. Studies conducted at the University of Ulm and the Fraunhofer Institute of Toxicology and Aerosol Research (Germany) found that pyrethrins persisted 60 hours after treatment on horizontal surfaces,⁵⁷ two weeks after treatment on airborne particles, and over two months in carpet dust.⁵⁸ (See Figure 7.)

Effects on Soil Fertility

Insecticides are generally not expected to have impacts on plants. However, they can indirectly affect plant growth if they change the growth or abundance of soil microorganisms that are important in the maintenance of soil fertility. Scientists at the University of Ibadan (Nigeria) showed that treatment of agricultural soils with pyrethrin caused an increase in the abundance of soil bacteria and a decrease in the abundance of soil fungi. In addition, the number of these species was less in treated soil than in

Figure 7
Persistence of Pyrethrins
after Treatment



Source: Berger-Preiß, E., K. Levssen, and A. Preiß. 1997. Analysis of individual natural pyrethrins in indoor matrices by HRG/ECD. *J. High Resol. Chromatogr.* 20: 284-289.

Pyrethrins persisted in carpet dust for over two months after treatment.

untreated soil. The end result was a reduction in the amount of the important soil nutrient nitrogen.⁵⁹ Another study, from the Central Rice Institute (India), showed that pyrethrin treatment of rice fields reduced the nitrogen-fixing ability of the soils as much as 80 percent.⁶⁰ Nitrogen fixation is the conversion (mostly by bacteria) of atmospheric nitrogen into a form that is usable by plants.⁶¹ ✻

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