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Reregistration Eligibility Decision for Nicotine

List B

Case No. 2460

Reregistration Eligibility Decision (RED) Document

For

Nicotine

Approved by: _____

Steven Bradbury
Director
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Date: _____

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Glossary of Terms and Abbreviations

AGDCI	Agricultural Data Call-In
ai	Active Ingredient
aPAD	Acute Population Adjusted Dose
AR	Anticipated Residue
BCF	Bioconcentration Factor
CFR	Code of Federal Regulations
cPAD	Chronic Population Adjusted Dose
CSF	Confidential Statement of Formula
CSFII	USDA Continuing Surveys for Food Intake by Individuals
DCI	Data Call-In
DEEM	Dietary Exposure Evaluation Model
DFR	Dislodgeable Foliar Residue
DWLOC	Drinking Water Level of Comparison.
EC	Emulsifiable Concentrate Formulation
EDWC	Estimated Drinking Water Concentration
EEC	Estimated Environmental Concentration
EPA	Environmental Protection Agency
EUP	End-Use Product
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FFDCA	Federal Food, Drug, and Cosmetic Act
FQPA	Food Quality Protection Act
FOB	Functional Observation Battery
G	Granular Formulation
GENEEC	Tier I Surface Water Computer Model
GLN	Guideline Number
HAFT	Highest Average Field Trial
IR	Index Reservoir
LC_{50}	Median Lethal Concentration. A statistically derived concentration of a substance that can be expected to cause death in 50% of test animals. It is usually expressed as the weight of substance per weight or volume of water, air or feed, e.g., mg/l, mg/kg or ppm.
LD_{50}	Median Lethal Dose. A statistically derived single dose that can be expected to cause death in 50% of the test animals when administered by the route indicated (oral, dermal, inhalation). It is expressed as a weight of substance per unit weight of animal, e.g., mg/kg.
LOC	Level of Concern
LOD	Limit of Detection
LOAEL	Lowest Observed Adverse Effect Level
MATC	Maximum Acceptable Toxicant Concentration
µg/g	Micrograms Per Gram
µg/L	Micrograms Per Liter
mg/kg/day	Milligram Per Kilogram Per Day

mg/L	Milligrams Per Liter
MOE	Margin of Exposure
MRID	Master Record Identification (number). EPA's system of recording and tracking studies submitted.
MUP	Manufacturing-Use Product
NA	Not Applicable
NAWQA	USGS National Water Quality Assessment
NPDES	National Pollutant Discharge Elimination System
NR	Not Required
NOAEC	No Observed Adverse Effect Concentration
NOAEL	No Observed Adverse Effect Level
OP	Organophosphate
OPP	EPA Office of Pesticide Programs
OPPTS	EPA Office of Prevention, Pesticides and Toxic Substances
PAD	Population Adjusted Dose
PCA	Percent Crop Area
PDP	USDA Pesticide Data Program
PHED	Pesticide Handler's Exposure Data
PHI	Preharvest Interval
ppb	Parts Per Billion
PPE	Personal Protective Equipment
ppm	Parts Per Million
PRZM/EXAMS	Tier II Surface Water Computer Model
Q_1*	The Carcinogenic Potential of a Compound, Quantified by the EPA's Cancer Risk Model
RAC	Raw Agriculture Commodity
RED	Reregistration Eligibility Decision
REI	Restricted Entry Interval
RfD	Reference Dose
RQ	Risk Quotient
SCI-GROW	Tier I Ground Water Computer Model
SAP	Science Advisory Panel
SF	Safety Factor
SLC	Single Layer Clothing
SLN	Special Local Need (Registrations Under Section 24(c) of FIFRA)
TGAI	Technical Grade Active Ingredient
TRR	Total Radioactive Residue
USDA	United States Department of Agriculture
USGS	United States Geological Survey
UF	Uncertainty Factor
UV	Ultraviolet
WPS	Worker Protection Standard

Abstract

This document presents the Environmental Protection Agency's (EPA's or the Agency's) decision regarding the reregistration eligibility of the registered uses of the active ingredient nicotine. The Agency conducted human health and environmental fate and effects risk assessments for nicotine non-food uses. The registrant of the sole remaining nicotine pesticide product requested the cancellation of its registration on February 25, 2008, to be effective on December 31, 2013, with existing stocks permitted to be sold by dealers and distributors for one additional year. The Agency has accepted this request in concept, and it is subject to notice and public comment. If public comment provides no information that causes the Agency to reconsider, the Agency may accept the cancellation request.

The assessment of risks for the pesticidal use of nicotine is unique in that much of the supporting data is drawn from the open literature, as opposed to studies conducted according to Agency guidelines, and the data that are available are not entirely well-matched to anticipated routes of exposure and use patterns for the nicotine pesticide. The lack of more relevant data adds considerable uncertainty to the risk assessment and would necessitate that the Agency call-in data from a range of guideline studies. Ultimately, the process the Agency undertook to assess risks and formulate reregistration eligibility decisions was overtaken by the registrant's request for cancellation. The Agency is finalizing this reregistration eligibility decision as a record of the database and methodologies that were used to assess nicotine and the Agency's preliminary conclusions about the risks associated with its use.

The sole remaining nicotine registration, for which cancellation has been requested, is a Restricted Use Pesticide used on greenhouse ornamentals, including poinsettias, bedding plants, and chrysanthemums to control whiteflies, aphids, and thrips. Nicotine has been known for its pesticidal properties for centuries, and came into common use in the U.S. about sixty years ago. Production and usage are now quite limited.

Using the limited available data, EPA has assessed the human health risks for the remaining nicotine registration and has concluded that risks for workers both during and after application, and for consumers of plants from treated greenhouses and members of the public who might be exposed to nicotine residues in treated greenhouses, are potentially of concern. Nicotine is not used on any food and feed crops so dietary risks have not been assessed. Because nicotine is used in greenhouses only, drinking water and ecological risks were not assessed for this use pattern, although the Agency did assess the ecological risks associated with another nicotine product used outdoors to repel vertebrate pests of ornamentals which has since been cancelled. The ecological risk assessment and an assessment of episodic ingestion of the nicotine repellant product are posted to the nicotine docket, as are the technical documents supporting the human health risk assessment for the nicotine greenhouse use.

I. INTRODUCTION

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) was amended in 1988 to accelerate the reregistration of products with active ingredients registered prior to November 1, 1984. The amended Act calls for the development and submission of data to support the reregistration of an active ingredient, as well as a review of all data submitted to EPA. Reregistration involves a thorough review of the scientific database underlying a pesticide's registration. The purpose of the Agency's review is to reassess the potential risks arising from the currently registered uses of a pesticide, to determine the need for additional data on health and environmental effects, and to determine whether or not the pesticide meets the "no unreasonable adverse effects" standard of FIFRA.

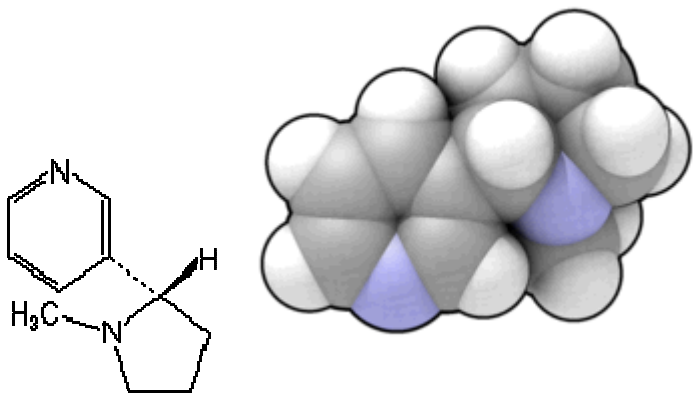
This document presents EPA's human health risk assessment. It consists of five sections. Section I (this section) contains the regulatory framework for reregistration and tolerance reassessment. Section II provides a description of the chemical and a profile of the use and usage of the chemical. Section III summarizes the human health risk assessment for pesticidal nicotine. Section IV presents the Agency's risk management decision. Section V addresses the obligations of the registrant pursuant to this RED, including mitigation measures the Agency believes need to be implemented during the phase-out period. The documents that support this RED and characterize the risks associated with nicotine products that recently have been cancelled are available in the public docket maintained electronically by the Federal government. All these documents can be accessed via the edocket website at www.regulations.gov under docket identification number EPA-HQ-OPP-2007-1019.

II. CHEMICAL OVERVIEW

A. Chemical Identity

Empirical Formula $C_{10}H_{14}N_2$

Molecular Structure



Common Name**:** Nicotine

Chemical Name**:**	3-(1-methylpyrrolidin-2-yl)pyridine; S-enantiomer
Synonyms**:**	Pyridine, 3-[(2S)-1-methyl-2-pyrrolidinyl]-; Pyridine, 3-(1-methyl-2-pyrrolidinyl)-, (S)-; L-Nicotine; Pyridine, (S)-3-(1-methyl-2-pyrrolidinyl); 1-Methyl-2-(3-pyridyl) pyrrolidine; Pyridine, 3-(1-methyl-2-pyrrolidinyl)-, (S); (S)-3-(1-Methyl-2-pyrrolidinyl)pyridine; (-)-Nicotine
OPP Chemical Code:	056702
CAS Number:	54-11-5
Molecular Weight, $g.mol^{-1}$:	162.234
Chemical Family:	Pyridine alkaloid
Technical Registrant**:**	None registered
Special Local Need**:**	None

B. Regulatory History

Nicotine, derived from the tobacco plant, has been used as a pesticide since at least the 15th century. Its use in the United States began expanding in the 1940s and 50s. By the 1990s, nicotine use dropped as new insecticides were registered (and continue to be registered) for the same crop/pest combinations. The last food use registrations of nicotine were cancelled in January 1994, and the tolerances associated with the last remaining food uses were revoked effective December 2005.

When the Agency began the reregistration process for nicotine, there were three active pesticide registrations containing the active ingredient. Early in the process, the registrant of two of these products indicated that it would request cancellation for one of them, EPA Registration Number 4-340, Bonide Tobacco Dust. As a result, the Agency did not initiate risk assessments for the corresponding use pattern.

In September 2007, Bonide formally requested the voluntary cancellation of its Tobacco Dust registration (EPA Registration Number 4-340) and also for its other nicotine registration (EPA Registration Number 4-465, Bonide Rabbit & Dog Chaser). Both of these products were registered for use outdoors, the first to control insect pests of ornamentals, and the second as a rabbit and dog repellant for ornamentals including turf. When Bonide indicated its intention to cancel the second of these two registrations, the Agency stopped work on aspects of the risk assessments corresponding to the applicable use pattern. The Agency has developed an environmental fate and ecological risk assessment document and a summary characterization of the risks from episodic ingestion of the Rabbit & Dog Chaser product. Although these documents do not figure in the Agency's conclusions about the remaining nicotine product, they are posted to the

electronic docket as part of the record for the nicotine pesticides. Potential risk concerns are identified in both the human health and ecological risk analyses for the outdoor use patterns.

After a public comment period on the cancellation requests in which no comments were submitted, the Agency issued a cancellation order for both Bonide registrations. The cancellations became effective March 5, 2008. Bonide has not manufactured its Tobacco Dust product for three or four years; there are no existing stocks in its possession. In accordance with its request, Bonide was granted 24 months after the effective date of cancellation to distribute or sell its existing stocks of the Rabbit & Dog Chaser product.

At present, Fuller Corporation has requested the voluntary cancellation of the sole active registration for nicotine, its Fulex Nicotine Fumigator (EPA Registration Number 1327-41). The Agency determined early in the reregistration process that ecological and drinking water assessments were not needed for this product, because of its limited usage and because it is used indoors only. The Agency did conduct a human health risk assessment for the Fulex product. While the assessment is characterized by a great deal of uncertainty, EPA has identified potential risks; these are discussed in this document and detailed in the supporting documents. Fuller Corporation requested the cancellation of its registration on February 25, 2008, to be effective on December 31, 2013, with existing stocks permitted to be sold by dealers and distributors for one additional year.

Nicotine has not been registered for use on food crops or crops contributing to livestock diet for many years. Tolerances for residues of nicotine on or in cucumber, lettuce, and tomato at 40 CFR180.167 expired as of December 4, 2005. Citations for the expired tolerances will be removed from the Code of Federal Regulations through the rule-making process.

C. Use Profile

The following information is based on the currently registered uses of nicotine.

Type of Pesticide:	Insecticide
Use Sites:	Ornamental plants in greenhouses only, especially poinsettias, and including annual bedding plants and chrysanthemums. Should not be used on violets.
Target Pests:	Adult thrips, whiteflies, and aphids.
Formulation Type:	Smoke generating canisters (12 and 24 oz., 12/pkg.), 13.4% ai
Method and Rates of Application:	Nicotine and inerts are packaged in metal cans with sparklers included. Sparkler is lit and inserted into canister; smoke escapes from canister. A 12 oz. can treats 20,000 cubic ft. After the fumigation is completed, typically the next morning after a late day application, the greenhouse is vented. Ventilation requirements are specified by the WPS. Passive ventilation is accomplished by

	opening greenhouse vents for approximately 2 hours; active ventilation is accomplished by opening vents and running venting fans for about 1 hour. Vents may be opened and fans started manually or remotely.
Timing: and Application Parameters:	Multiple applications may be needed, typically up to three times per season, at three to 12-day intervals. For plant production facilities, the product is used mostly at the end of the growing cycle before shipping to retail outlets. Use declines from mid-June to mid-September, and peaks again with poinsettia finishing.
Use Classification:	This product is designated a Restricted Use Pesticide due to very high acute inhalation, oral, dermal, and eye toxicity to humans.

D. Usage of Pesticide

Since there is only one nicotine product, volume of production is CBI.

E. Tolerances

Tolerances for residues of nicotine in or on cucumbers, lettuce, and tomatoes are listed at 40 CFR 180.167, and expired effective December 4, 2005. Citations for the expired tolerances will be removed from the Code of Federal Regulations through the rule-making process.

F. Benefits

In contrast to some other treatments, there are no reports of nicotine resistance in whitefly populations. The smoke provides full coverage for overhead hanging baskets, under benches, in dense plant canopies, etc. Smoke does not discolor blooms as liquid applications might. Using a smoke formulation, rather than a manual spray operation, can reduce the possibility of heat stress in handlers as applications typically are made at night, when greenhouse temperatures are lowest.

III. SUMMARY OF NICOTINE RISK ASSESSMENTS

A. Human Health Risk Assessment

The Agency's findings on the human health risks associated with the use of the sole remaining nicotine registration are detailed in the docket in the document, "Nicotine and derivatives: PC Code: 056702," with attachments, dated March *XX*, 2008. The risk assessment summarized below forms the basis of this RED.

B. Toxicology

While nicotine itself has been the subject of extensive research, guideline studies appropriate to its pesticidal use are lacking. For the most part, this assessment relies on endpoints derived from published data in the open literature. The Agency searched a wide variety of databases to identify potentially relevant toxicity literature, including Science Direct, PubMed, ToxNet, ToxLine, a report of the Surgeon General, and records from the International Programme on Chemical Safety.

The utility of the open literature for hazard characterization in this risk assessment is very limited. Ideally, pesticide risk assessments rely on studies that approximate the potential exposure routes. For the purposes of this risk assessment, the potential routes of exposure are inhalation, dermal, and to a lesser extend oral; the Agency is able to relate exposures in oral studies to other exposure routes with the use of generally accepted assumptions. Unfortunately, the open literature includes only a few studies in which nicotine was administered orally or by inhalation. These studies were considered by the Agency for this assessment. Very few of the open literature studies employed the dermal route, and these studies were qualitative and did not provide a quantitative measure of the degree of toxicity. All studies surveyed by the Agency were used collectively to characterize the toxicity of nicotine, but only studies with the appropriate routes of exposure were used in endpoint selection for this risk assessment.

Nicotine is acutely toxic (Category I) by all routes of exposure (oral, dermal, and inhalation). The LD_{50} of nicotine is 50 mg/kg for rats and 3 mg/kg for mice. A dose of 40–60 mg can be a lethal dosage for adult human beings and doses as low as 1-4 mg can be associated with toxic effects in some individuals. Nicotine is an agonist at nicotinic receptors in the peripheral and central nervous system

The Agency selected a subchronic oral rat toxicity study conducted with nicotine hydrogen tartrate (Yuen *et al*. 1995) as a basis for the episodic oral, dermal, and inhalation toxicity endpoints. In this study, nicotine was administered to pregnant and non-pregnant female rats in the drinking water for 10 days at doses equivalent to 1.25 and 2.5 mg/kg/day. The animals exhibited mild fatty change, mild focal necrosis and mild dark cell change, with effects on the mitochondria, in a dose proportional manner. Effects at the lower dose were not statistically significant, so the NOAEL was identified as 1.25 mg/kg/day; the LOAEL was identified as 2.5 mg/kg/day. The NOAEL from this study was selected for the assessment of short- and intermediate-term human health risks associated with the current nicotine use pattern.

According to the International Programme on Chemical Safety and other authorities, nicotine is neither an initiator nor a promoter of tumors in rodents.

The Agency determined that the appropriate margin of exposure for human health effects is 1000—10X for inter-species extrapolation, 10X for intra-species variability, and 10X for database uncertainty (10X).

C. Human Health Risk Characterization

1. Occupational Risk

Workers can be exposed to nicotine from the Fulex product through application and by post-application activities in treated areas. The occupational handlers of nicotine are the certified applicators (and those under their direct supervision) who apply nicotine and re-enter a greenhouse to operate ventilation equipment and clean-up canisters after deployment. Post-application workers include those who water, pack, prepare for shipment, or otherwise handle treated plants.

No nature of the residue data are available for the unique smoke-generator application method of nicotine, which appears to alter the physical state of the active ingredient and may result in the generation of nicotine reaction products and degradates. All potential combustion products and degradates of nicotine from the Fulex product are accounted for in the occupational exposure assessments and the Agency has assumed that they are toxicologically equivalent to the parent.

Occupational risk is measured by a Margin of Exposure (MOE) which determines how close the occupational exposure comes to the selected No Observed Adverse Effect Level (NOAEL). For nicotine, risks of concern are those that fall below the MOE of 1000. For workers entering a site to perform post-application tasks with a potential for dermal exposure, Restricted Entry Intervals may be calculated to determine the minimum length of time required before workers or others are allowed to reenter (in this case, at an interval when the MOE approaches 1000). For post-application inhalation exposures, there is no one time period of restricted entry after nicotine application, but the ventilation criteria of the Worker Protection Standard must be satisfied before post-application activities can resume.

2. Dietary and Drinking Water Risk

There are no registered food uses for nicotine, and it is used in greenhouses only. Dietary and drinking water exposures are not expected and were not assessed.

3. Residential Risk

The sole currently registered nicotine product is a Restricted Use Pesticide that must be applied by a properly certified applicator or subordinate and is used only in greenhouses. The Agency believes that it is unlikely that the product is used in private greenhouses, but the current label does not prohibit such use.

4. Risk to Consumers of Plants Treated with Nicotine

Based on the potential post-application risk to greenhouse workers who handle plants from greenhouses treated with nicotine (discussed later in this document), the Agency

believes there also is a potential for risk to consumers who enter a greenhouse soon after treatment with nicotine to purchase plants. The current label does not prohibit retail sales of treated plants for a set interval after nicotine application.

5. Aggregate Risk

Exposures contributing to aggregate risk are dietary, drinking water, and residential/ consumer exposures. Dietary and drinking water exposures for the current nicotine use pattern are not likely. Thus, only risks to residents and retail consumers have been assessed.

6. Exposure estimates for occupational handlers

Handler exposures to nicotine are expected to be short- or intermediate-term in length; since the endpoint for either exposure category is the same, only one set of values is reported.

The extent of a handler's dermal exposure to nicotine from the Fulex product is assumed to be small relative to the potential inhalation exposure. A dermal exposure assessment for handlers was not performed. Inhalation exposure estimates in this risk assessment are based on maximum theoretical air concentration calculations and default assumptions.

Duration of exposure is directly proportionate to the number of canisters of the Fulex product that must be deployed and retrieved after application by the handler. The exposure assessment is based on exposure times of 30 minutes to represent small greenhouses and 60 minutes to represent large greenhouses.

Inhalation dose estimates are based on theoretical air concentration of nicotine in a greenhouse when applied according to label directions, an exposure time of 30 or 60 minutes (small and large greenhouses; see above), a standard adult breathing rate of one cubic meter per hour and the default adult body weight of 70 kg (about 150 lbs). The dose is adjusted for the levels of protection provided by the different types of respiratory protection, and the Agency has estimated risks for individuals using different types of respiratory protection.

7. Risk estimates and discussion

Risk estimates based on the above-mentioned variables and default values are captured in Table 1. An MOE of 1000 or above is considered protective of human health in this context. MOEs in boldface represent risks potentially of concern.

Table 1. Short-Term Occupational Handler Inhalation Risk Estimates

Respirator type	Exposure time (per day)	Inhalation Dose (mg/kg/day)	Inhalation MOE
Baseline No Respirator	30 minutes	0.57	**2**
	60 minutes	1.14	**1**
PF10 Respirator Half-face organic-vapor-removing respirator providing 90% protection	30 minutes	0.057	**22**
	60 minutes	0.114	**11**
	<1 min.	0.00125	1000
PF50 Full-face organic-vapor-removing respirator providing 98% protection	30 minutes	0.01	**125**
	60 minutes	0.02	**63**
	~3 min.	0.00125	1000
PF10,000 Self-contained breathing apparatus (SCBA) providing 99.99% protection	60 minutes	0.0001	12500

The product label requires that handlers wear PPE including a respirator with either an organic vapor cartridge with a prefilter approved for pesticides or a canister approved for pesticides. The label does not specify half-face or full-face respirators.

Risk estimates based on the limited available data and maximum theoretical air concentration exceed levels of concern for handlers in small and large greenhouses, with exposure times of 30 and 60 minutes, respectively, and wearing half- or full-face respirators with the specifications detailed in the table above. Actual exposure times for Fulex applicators probably are shorter than 30 and 60 minutes, and more than the one or three minutes for which MOEs also are calculated.

This method of estimating risk assumes that the handler is exposed to the maximum possible concentration of nicotine in the greenhouse, when it is reasonable to assume that application activities are complete before the cans have released their entire nicotine contents into the greenhouse air. Thus, actual exposures are likely to be less than the inhalation doses shown in Table 1.

8. Occupational post-application exposure estimates

There is potential for both dermal and inhalation post-application exposures to workers, as some residues will settle on the greenhouse surfaces and plant leaves, and some will remain suspended in the air or subsequently become re-suspended.

Dermal exposures were estimated using transfer coefficients tasks representing different levels of exposure, according to the document "Science Advisory Council for Exposure: Agricultural Reentry Task Force Ornamental Plants Transfer Coefficients, April 2002." These coefficients, representing the rate of transfer of residues from surfaces to skin, vary

for different tasks depending on the amount of contact between the worker and the surfaces. Tasks can be designated as low or high exposure depending on the amount of contact.

Table 2. Post-application dermal transfer coefficients for greenhouse ornamentals

Transfer Coefficients (cm^2/hr)	**Example activities**
175 ("low exposure")	greenhouse hand pinching ornamentals; nurseries activities
400	moving plants from greenhouse to trucks, reorganizing gallon pots or containers
5100 ("high exposure")	hand-harvesting cut flowers

The exposure assessment is also based on a number of other assumptions:

Exposure was assessed at an application rate of 2.178 lb ai/A, based on a 10-foot greenhouse ceiling height and application information from the product label, converted to pounds of ai per acre.

Estimates were based on an 8-hour work day, and a body weight of 70 kg, and absorption of 100% of the nicotine on skin.

The Agency assumed that the fraction of residue retained on foliage which is available for transfer to skin is 20% on the day of application, and dissipates at the rate of 10% a day per standard values established by HED's Science Advisory Council for Exposure.

Table 3. Nicotine post-application dermal risk estimates for greenhouse workers

Days after treatment	**Dermal Dose (mg/kg/day)**		**Dermal MOE**	
	Low exposure activity	**High exposure activity**	**Low exposure activity**	**High exposure activity**
0	0.0976	2.844	**13**	**<1**
3	0.0712	2.075	**18**	**<1**
40	0.00144	0.042	868	**30**

To estimate inhalation exposure for workers engaged in post-application activities, the Agency calculated air concentrations expected when treated greenhouses are ventilated as required by the WPS. The WPS allows a number of different ways that a greenhouse may be properly ventilated before workers can re-enter. For this assessment, the Agency assumed a ventilation operation that results in 10 air changes. The Agency assumed an 8-hour workday, and standard body weight and breathing rate. Estimated according to these parameters, the post-application inhalation risk estimate for greenhouse workers is an MOE of 3049. Post-application worker inhalation is not a risk of concern for nicotine used in the greenhouse.

IV. RISK MANAGEMENT DECISION

Rather than develop data to better characterize actual risks, the registrant has requested the cancellation of the sole active nicotine registration, with cancellation effective on December 31, 2013, and existing stocks permitted to be sold by dealers and distributors for one additional year. The Agency intends to grant that request unless public comment warrants reconsideration.

The Agency believes that a phase-out is warranted in light of the extremely low volume of nicotine pesticide use, the niche benefits associated with the greenhouse use, and implementation of interim labeling to reduce the potential for exposure and reduce risk during the phase-out period. The registrant has committed to submit, for Agency approval and within three months of the date of this RED, revised labeling to address our mutual understanding of risks of concern. This labeling will prohibit 1) the use of nicotine on plants grown for cut flowers, 2) nicotine use in non-commercial greenhouses, and 3) the retail sale of treated plants within 24 hours after nicotine application. The Agency believes that these measures are sufficient to address the exposures to individuals at risk--greenhouse workers who hand-cut flowers, those who spend time in private greenhouses, and people, including children who come into contact with treated plants via retail sale.

If comments received during the comment period on the notice of receipt of request for voluntary cancellation warrant a reconsideration of the request or the Agency's risk management decision, there are a number of data requirements that would attach to the continued registration of the existing Fulex product, or any new uses. These data gaps, as well as the risks, benefits, and interim labeling requirements are discussed below.

A. Risks of Concern

The Agency has assessed the risks associated with the use of the sole remaining nicotine registration. The certainty of the conclusions drawn from these assessments is limited by a lack of critical data, including guideline study-generated data that address the toxicology of nicotine itself when test animals are exposed via routes of exposure relevant to the use pattern. The fate of nicotine upon deployment from the smoke-generating canister and how residues in the greenhouse dissipate over time are not known and not supported by empirical data.

Using the limited available data and protective assumptions, the Agency has identified potential risks of concern in several areas: residents exposed to nicotine from its use in private greenhouses, people who purchase and handle treated plants from retail establishments, occupational handlers, and workers who are exposed during post-application activities. Because nicotine is not used on food or feed crops, and is only applied in greenhouses, dietary risks and risks to wildlife are not expected nor assessed.

The Agency believes that the risks of concern identified for mitigation in this RED (and described below) generally tend toward overestimation because of the use of conservative assumptions. The use of these assumptions, mainly for estimating exposures, adds uncertainty to the calculated risk estimates; nevertheless, we believe that the risk estimates indicate that risk mitigation is warranted. The registrant elected not to develop the data that would be needed to conduct a more certain assessment of the risks and chose to request a voluntary phase-out instead. The Agency has determined that the 5-year phase-out requested by the registrant is acceptable, as long as the risk mitigation detailed in this RED is implemented in the interim before cancellation becomes effective.

1. Handler Risks

In the context of the limited data available for assessment, the Agency has identified risk estimates above levels of concern for occupational handlers of the nicotine product, but a definitive assessment of handler risks is precluded by the lack of conclusive information about applicator exposures, including the time spent deploying canisters and how much nicotine from the canisters is in the air that applicators breathe.

The duration of handler exposure during deployment of the canisters probably varies quite a bit in actuality, but the 30 and 60 minutes defaults used in this assessment likely are substantial overestimates that result in overestimates of risk. The registrant has submitted a self-directed study of these potential exposure times that, while not meeting Agency standards, suggests that handler exposure durations are much shorter.

The methodology the Agency employed for estimating concentrations of nicotine in greenhouse air in the absence of empirical data also tends to lead to an overestimation of handler exposures, since the entire contents of the Fulex canister are not instantaneously released as the handler lights the sparkler. The applicator is instructed to move away from the container as soon as it is lit and to repeat with each successive canister while moving toward the greenhouse exit, so applicator exposure to nicotine released from the container right after ignition should be minimized.

Because of the uncertainties in the assessment that indicate risks to handlers above levels of concern, and the tendency of the methodologies used by the Agency in the absence of empirical data, the Agency believes that actual handler risk is likely to be considerably lower than the risk estimates. The current label requirements for PPE, including the requirement that a handler must wear a respirator with either an organic vapor cartridge and a prefilter approved for pesticides, or a canister approved for pesticides, remain in effect, but no additional protective measures are deemed necessary.

2. Mitigation of Post-application Risks for Occupational Workers

In the absence of chemical-specific information, estimates of worker post-application dermal exposures have been based on important assumptions that tend to result in overestimates of exposure. For example, it is assumed that all the nicotine from the Fulex containers is released and comes to rest on greenhouse surfaces, and on the day of

application, 20% of that amount is available on foliage for contact with skin. The rate of dissipation of nicotine in the greenhouse after application and the dermal absorption rate are based on standard assumptions rather than the particular characteristics of nicotine; the Agency uses conservative assumptions in order to avoid underestimating real risk.

Given these considerable uncertainties and the tendency of exposure to be overestimated, the Agency believes that the MOEs calculated for greenhouse tasks of different intensity and different intervals after application are probably too low, but that hand-harvesting of cut flowers, while not a major use site for nicotine, has the highest potential for exposure relative to other greenhouse tasks. While the magnitude of risk for all the post-application activities is likely to be less than estimated, the Agency believes it is prudent to eliminate the highest exposure scenario for nicotine-treated plants during the phase-out period. In the interim before cancellation, labels of the Fulex product will be amended to prohibit the use of nicotine on plants grown for cut flowers.

3. Mitigation of Residential/Consumer Risks

The Agency believes that it is unlikely that nicotine is used in non-commercial greenhouses. To the extent that it may be, owners of private greenhouses and those that enter such greenhouses (including children) after nicotine has been applied by a Certified Applicator would not necessarily have an understanding of precautions that should be taken to limit exposure. Prohibiting nicotine use in non-commercial greenhouses will eliminate risks to people who own private greenhouses, live in close proximity to such greenhouses, or spend time in them.

The Agency has based its concern about people who shop for and handle treated plants on the risk estimates for greenhouse workers engaging in post-application tasks. Risks to the workers are probably overestimated based on the factors discussed in Section 2 above. In addition, worker risk estimates are based on an 8-hour workday, which likely exceeds the amount of time a consumer would spend in contact with treated plants.

People who enter treated greenhouses after application (and after the ventilation criteria have been met) and people who handle or come in contact with treated plants both in retail greenhouses and once they have been purchased may include consumers themselves and the children who accompany them, help with planting, and play around such plants placed in residential gardens. The differential risks to children from exposure to nicotine residues have not been quantified, but it seems prudent to limit their exposure. While the rate of dissipation of nicotine residues in treated greenhouses and on treated plants is not known, it is assumed that residues will decline over time, and may impart be removed from foliage and other surfaces during daily watering. It is anticipated that closing treated greenhouses to consumers and keeping treated plants out of retail sale for a short period of time is not only prudent but will not cause an undue burden to businesses. Potential risks to consumers of treated plants and children who might also be exposed to treated plants will be reduced by prohibiting the retail sale of treated plants within 24 hours after nicotine application.

B. Benefit Considerations

The use of the nicotine product is very limited, but several growers and applicators have contacted the Agency to show support for the product, which they indicate is easier to use than the alternatives; takes less time to apply and reduces the amount of time an applicator needs to spend in hot protective clothing; and provides ready coverage of plants in harder-to reach places, such as overhead hanging baskets and pots under greenhouse benches.

The registrant has noted that certain strains of whitefly are developing resistance to pesticides. Nicotine is effective against this "Q-biotype" whitefly, but the Agency believes that there are a number of pesticidal alternatives to nicotine that are also effective and do not promote resistance.

C. Tolerances

The tolerances for nicotine have been reassessed, and revocation of these tolerances (for residues in cucumber, lettuce, and tomato) was announced in a Federal Register notice on July 23, 2004 (69 FR 43924, http://www.epa.gov/fedrgstr/EPA-PEST/2004/July/Day-23/p16718.htm) after termination of the last food uses of nicotine. Per that notice, the tolerance revocations became effective on December 4, 2005. Citations for the expired tolerances will be removed from the Code of Federal Regulations through the rule-making process.

D. Data Gaps

The database for nicotine is incomplete. Data that would be needed to refine the Agency's understanding of the risks associated with the use of nicotine include:

830 series	Special study; fate of nicotine released from smoke-generating canisters
870.1100	Acute Oral Toxicity
870.1200	Acute Dermal Toxicity
870.1300	Acute Inhalation Toxicity
870.2400	Primary Eye Irritation
870.2500	acute dermal irritation - rabbit
870.2600	skin sensitization
870.3200	21-day dermal toxicity study in rats
870.3465	90-day inhalation study (duration reduced to 21 days)
870.3700a	Prenatal developmental - rodent
870.3800	Reproduction and fertility effects
870.6200a	acute neurotoxicity screening battery
870.3700a	prenatal developmental – rodent
870.3700b	prenatal developmental – non-rodent

For outdoor uses--environmental fate and effects data (including acute and chronic toxicity data for terrestrial and aquatic wildlife, and data on effects to aquatic plants and honeybees).

V. ACTIONS REQUIRED OF THE REGISTRANT

The registrant has agreed to interim labeling as noted above and will submit revised labeling within 90 days of publication of this RED.