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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

Fax-On-Demand
Telephone: (202) 401-0527
Item: 6101

September 4, 1997

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

Pesticide Registration (PR) Notice 97-3

NOTICE TO MANUFACTURERS, FORMULATORS, PRODUCERS AND REGISTRANTS OF PESTICIDE PRODUCTS

ATTENTION: Persons Responsible for Registration of Pesticide Products

SUBJECT: Guidelines for Expedited Review of Conventional Pesticides under the Reduced-Risk Initiative and for Biological Pesticides

I. PURPOSE

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) as amended by the Food Quality Protection Act of 1996 (FQPA) requires the Environmental Protection Agency (EPA) to develop procedures and guidelines for expedited review of any pesticide. These procedures and guidelines must be in place within one year after the date of enactment of the FQPA (by August 3, 1997). EPA has already established a Reduced Risk Initiative for conventional pesticides, has formed the Biopesticides and Pollution Prevention Division to review biological pesticides and has established the Antimicrobial Division to review antimicrobial pesticides. The purpose of this PR Notice is to provide the process and criteria to guide applicants in developing their submissions to these programs.

This PR Notice supersedes the reduced-risk criteria published in Federal Register Notices 57 FR 32140, July 20, 1992 and 58 FR 5854, January 22, 1993 and PR Notice 93-9, July 21, 1993. In addition, it defines the types of pesticide products reviewed by the Biopesticides and Pollution Prevention Division and describes how an applicant can apply for biochemical pesticide classification.

The goal of the Reduced-Risk Pesticide Initiative and the Biopesticides and Pollution Prevention Division is to encourage the development, registration and use of lower-risk pesticide products which would result in reduced risks to human health and the environment when compared to existing alternatives. The major incentive which EPA offers for these pesticides is expedited registration review. The major goal of the Antimicrobial Division is to provide expedited review of all types of antimicrobial registration actions.

II. APPLICABILITY

This notice applies to all applicants for initial registration and amended registration for conventional pesticides, as described more fully in Sections IV-X, and for biological pesticides, as described in Section XI. The term "conventional pesticides" as used in this notice includes all pesticides other than biological pesticides and antimicrobial pesticides (as defined in FQPA). Since certain pesticide products, such as wood preservatives and antimicrobials, are not defined as antimicrobial products in FQPA but are handled in the Antimicrobial Division, for the purposes of this notice they are considered conventional pesticides.

III. EFFECTIVE DATE

This PR Notice is effective immediately.

IV. BACKGROUND ON THE REDUCED-RISK INITIATIVE

In July 1992, the Office of Pesticide Programs (OPP) published a Federal Register notice announcing the need for incentives for the development and registration of reduced-risk pesticides. In a subsequent Federal Register notice (January 1993) OPP announced the initiation of the Reduced-Risk effort, and in July 1993 OPP published PR Notice 93-9 which provided interim reduced-risk criteria and guidance for submissions.

Since July 1993, applicants have sent thirty-nine new chemical or new use submissions to OPP for consideration as reduced-risk pesticides. Of the thirty-nine, twenty-two have been accepted by OPP as reduced-risk candidates; and sixteen have been rejected. Of the twenty-two accepted reduced-risk submissions, fourteen have been registered. The following is a list of the registered pesticides by accepted common names (if available) and their trade name (in parenthesis):

(1) Hexaflumuron (Recruit) - below ground bait station termiticide

(2) Flumiclorac-pentyl (Resource) - post emergent herbicide on corn, soybeans

(3) Methyl Anthranilate (Rejex-It) - bird repellent on cherries, grapes, blueberries, forestry

(4) Tebufenozide (Confirm) - insecticide on walnuts

(5) Hymexazol (Tachigaren) - fungicide seed treatment on sugar beets

(6) Fludioxonil (Maxim) - fungicide seed treatment on corn, sorghum

(7) (Cadre) - herbicide on peanuts

(8) (Mefenoxam) - fungicide on multiple crops

(9) Spinosad (Spinosad) - insecticide on cotton

(10) Azoxystrobin (Heritage) - fungicide on turf

(11) Alpha-Metolachlor (CGA 77102) - herbicide on multiple crops.

(12) Hexaflumuron (Recruit) - above ground bait station new use termiticide

(13) Imazamox (Raptor) - herbicide on soybeans

(14) Azoxystrobin (Heritage) - fungicide on grapes, bananas, peaches, tomatoes, pecans and peanuts

The major advantage for reduced-risk pesticides is expedited registration review. For FY95 and FY96 (prior to the passage of FQPA in August 1996) the average total time required to register a new conventional pesticide was thirty-eight months. For reduced-risk pesticides the average total time for registration was only fourteen months. Since passage of FQPA three new AI, reduced-risk pesticides were registered in seventeen, eighteen and seventeen months, somewhat longer than the pre-FQPA average but still substantially shorter than the conventional pesticide times. The faster registration times reflect, in part, the expedited review status granted reduced-risk actions. Not only is the initial submission granted a high review priority but also any resubmission that may be necessary.

If the applicant is simultaneously seeking registration in Canada, and if the application has been determined by Canada to be complete, the reduced-risk action can also qualify for work-sharing between the two countries. While this work-sharing program is still in the "pilot" stage, it could result in further reduced review times and greater harmonization.

V. CHARACTERISTICS OF ACCEPTABLE AND UNACCEPTABLE SUBMISSIONS FOR THE REDUCED-RISK INITIATIVE

OPP has assessed fourteen of the twenty-two reviews conducted by the Reduced Risk Committee of submissions that were determined to be reduced-risk. Those factors that most significantly contributed to EPA's decision to grant reduced risk status are summarized below in descending order:

- human health effects
  - very low mammalian toxicity

- toxicity generally lower than alternatives (10-100X)
- displaces chemicals that pose potential human health concerns [e.g., organophosphates (OPs), probable carcinogens (B2s)]
- reduces exposure to mixers, loaders, applicators and reentry workers

o non-target organism effects (birds)

- very low toxicity to birds
- very low toxicity to honeybees
- significantly less toxicity/risk to birds than alternatives
- not harmful to beneficial insects, highly selective pest impacts

o non-target organism effects (fish)

- very low toxicity to fish
- less toxicity/risk to fish than alternatives
- potential toxicity/risk to fish mitigatable
- similar toxicity to fish as alternatives but significantly less exposure

o groundwater (GW)

- low potential for GW contamination
- low drift, runoff potential
- runoff mitigatable

o lower use rates than alternatives, fewer applications

o low pest resistance potential (i.e., new mode of action)

o highly compatible with IPM

o efficacy.

OPP has also assessed eleven of the sixteen reviews conducted by the Reduced Risk Committee of submissions that were determined not to be reduced-risk. Those factors that most significantly contributed to an unacceptable decision by the committee are summarized below in descending order:

o human health effects

- inadequate/inappropriate comparisons with alternatives
- inadequate documentation of effects
- human health risk reduction case weak

- risk reduction case inadequate when compared to alternatives

o non-target organism effects (birds and fish)

- toxic to birds
- toxic to fish
- risk reduction case inadequate when compared to alternatives

o potential GW problems

o unlikely to displace higher risk alternatives

o lack of efficacy data

o phytotoxicity.

This survey of past decisions should assist future applicants in preparing their submissions.

VI. PROCEDURES AND GUIDELINES FOR EXPEDITED REVIEW OF CONVENTIONAL AND ANTIMICROBIAL PESTICIDES

A. Background

In general, FIFRA section 3(c)(3)(A) requires EPA after receipt of an application for registration of a pesticide "as expeditiously as possible" either to register it or to notify the applicant that the application does not comply with the Act. FIFRA also establishes expedited review procedures for a variety of Agency activities associated with the registration of pesticides, including expedited review for certain end-use pesticides that are identical or substantially similar to currently registered pesticides ("me too" registrations) as provided in FIFRA section 3(c)(3)(B)(II), and for antimicrobial pesticides as provided for in FIFRA section 3(h)(2). EPA also has several programs to expedite the registration process for biological pesticides by the Biopesticides and Pollution Prevention Division, antimicrobial pesticides by the Antimicrobial Division and fast track procedures to expedite the registration of certain amendments to existing conventional pesticide registrations. As a result of these programs, EPA is already expediting many pesticide applications for registration.

FIFRA section 3(c)(10) establishes an expedited review for applications for registration and amendments to registrations for pesticides that "may reasonably be expected to accomplish one or more of the following:

(i) Reduce the risks of pesticides to human health.

(ii) Reduce the risks of pesticides to nontarget organisms.

(iii) Reduce the potential for contamination of groundwater, surface water or other valued environmental resources.

(iv) Broaden the adoption of integrated pest management strategies, or make such strategies more available or more effective."

The statute does not establish deadlines for review of registration applications or amendments that meet the above criteria. Section 3(c)(10), however, requires EPA to notify the applicant whether the application for expedited review is complete no later than 30 days after receipt of the application.

B. Procedures

EPA intends to establish a two-step procedure for expedited review pursuant to FIFRA section 3(c)(10).

1. Step One - Application. For step 1, the Agency will determine whether an application for registration or amended registration qualifies for expedited review based upon whether use of the pesticide proposed by the application may reasonably be expected to accomplish one or more of the criteria listed in Section VI.A. above.

To initiate the process, the applicant must submit an application for expedited review demonstrating how the use of the pesticide may reasonably be expected to accomplish one or more of the criteria listed in section VI.A. above. The applicant also must submit a reduced-risk rationale pursuant to the guidelines and procedures specified in sections VII - IX of this notice. The step 1 rationale may be a sentence or a paragraph in the reduced-risk rationale summary as long as the claims are documented elsewhere in the reduced-risk rationale.

Certain types of pesticide applications for registration and amended registration already receive expedited review pursuant to existing Agency programs. Because the Agency is already expediting review of these registrations, it is not necessary to include them in the review program established pursuant to FIFRA section 3(c)(10). Applications that already receive expedited review include applications for registration or amended registration for biological or antimicrobial pesticides, "me-too" applications for registration or amended registrations of end-use pesticides under FIFRA section 3(c)(3)(B)(I) that are identical or substantially similar to other EPA registered pesticide products, and applications for certain pesticides under FIFRA section 3(c)(3)(B)(II).

The FQPA amendments require EPA to make expedited decisions on antimicrobial pesticides as defined in FIFRA section 2(mm). Specifically, FIFRA section 3(h)(2) establishes goals for the time periods during which EPA must review different types of applications for

antimicrobials covered by the statutory definition and make decisions whether to approve or deny the applications. Generally, these review and decision deadlines are 30% to 60% shorter than historic Agency performance in processing such applications.

While FIFRA antimicrobial review deadlines do not become legally binding until May 1998, as a matter of policy, the Agency has committed to and, in fact, is meeting the goals specified in FIFRA section 3(h)(2) as well as the expedited deadlines already mandated in FIFRA section 3(c)(3)(B). For every application received by the Agency since November 1, 1996, the Agency has made a registration decision within the review periods provided by the statute. EPA will continue to expedite review of applications for registrations and amendments to registrations for antimicrobial pesticides pursuant to its commitment.

The Agency's improved performance in review of antimicrobials is the result of several new initiatives. First, EPA has established within the Office of Pesticide Programs a new Antimicrobials Division (AD) that is responsible for all regulatory decisions relating to antimicrobial and related pesticides. In addition to regulatory staff, the new AD organization includes scientific personnel capable of performing most of the analyses needed to make a registration decision. Thus, AD is capable of providing "one-stop shopping" for registration decisions. Second, the new AD management team has instituted a number of process improvements, including a dedicated expedited review team of "me-too" applications, that have resulted in a significantly improved performance.

Thus, because EPA's current organizational and resource allocations, and process improvements are providing expedited review for antimicrobials, all types of applications for antimicrobial pesticides (as defined in FQPA) will be outside the scope of this PR Notice.

What types of applications for expedited review will the Agency accept? An application for expedited review may be submitted only for the following types of actions:

(a) an application to register a conventional pesticide that contains an active ingredient not contained in any currently registered pesticide, provided the pesticide is not a biopesticide or an antimicrobial pesticide (as defined in FQPA). [See sections VII through IX for reduced-risk rationale guidelines]; or

(b) an application to amend the registration of a currently registered conventional pesticide for an additional new use, provided the pesticide is not a biopesticide or an antimicrobial pesticide (as defined in FQPA). [See sections VII through IX for reduced-risk rationale guidelines]; or

(c) a non-fast-track application for registration of a new formulation provided the pesticide is not a biopesticide or an antimicrobial pesticide (as defined in FQPA). [See section X for expedited review rationale guidelines].

2. Step 2 - Reduced-Risk Determination If an application for expedited review qualifies under step 1, the Agency will expedite the review of the reduced-risk rationale presented by the applicant to determine whether the pesticide qualifies under the reduced- risk criteria described in sections VII and X below. The Agency's Reduced-Risk Committee will expedite the review of the reduced-risk rationale and complete its review within thirty days of receipt of a complete reduced-risk rationale. If the Agency decides that a pesticide qualifies for reduced-risk status, then it will further expedite review of the remainder of the application for registration or amended registration as described in section IV of this notice.

If the Agency denies a submission reduced-risk status, applicants will be given only one opportunity to rebut this decision, and the applicant will have four weeks to resubmit their rebuttal. Due to limited program resources, the Agency can only allow one opportunity to rebut a decision. Pesticides that EPA determines do not qualify for reduced-risk status during step 2 will be processed in accordance with existing Agency procedures.

VII. GUIDELINES FOR REDUCED RISK RATIONALES

While participation in the reduced-risk pesticides program is voluntary, those who elect to participate must fully address all of the following areas: (a) executive summary, (b) human health effects; (c) environmental fate and effects; (d) other hazards; (e) risk discussion (f) pest resistance and management (e.g., IPM); and (g) comparative performance, (h) other information and how application complies with FQPA. The Agency will consider all of these areas in determining the acceptability of these applications. However, these may not be the exclusive factors in all cases. If an applicant identifies additional criteria that substantiate the argument that their product is indeed a reduced-risk pesticide, then EPA invites the applicant to submit a rationale with any supporting data to verify such a claim. The Agency will consider this additional information.

An applicant's documentation must contain both a discussion of the inherent reduced-risk properties of their product, as well as a comparison of those properties with the properties of the commonly-used alternatives where appropriate. Comparisons must be made to conventional chemical pesticides, antimicrobial pesticides, biological pesticides, and cultural practices currently being used for pest control at the same use site(s) and for the same pest(s).

Please note that the Agency does not expect the applicant to perform any additional testing to derive the data necessary to develop rationales for the Reduced-Risk Program. The applicant must summarize all data in the applicant's possession or control or available through the open literature for the product being submitted to the Agency. If data addressing one of the stated factors has been developed, but is not required for registration of the pesticide in the United States, the applicant must provide a summary of these data as part of the Reduced-Risk Rationale. If any of the required information is not known, that fact must be noted in the rationale.

If the rationale does not include a discussion of each of these factors or provide reasoning as to why the factor should not be considered in the Agency's decision, OPP will consider the rationale to be incomplete and not responsive to this PR Notice. However, if the applicant believes that the factor does not apply to the new pesticide, the registrant must provide a short rationale describing this reasoning.

In situations where the Agency has already reviewed data on the active ingredient, the applicant should use the Agency's review to address the relevant factor(s). Applicants must also provide Master Record Identification (MRID) numbers for each study, where appropriate.

A. Executive Summary. Provide an executive summary that addresses the following considerations:

1. Chemical Name.

2. Chemical Abstracts Service Registry Number.

3. Chemical Structure.

4. Chemical Class or Family Name of the Active Ingredient.

5. Mode/Mechanism of Pesticidal Action for the Active Ingredient (if known).

6. Proposed Use Pattern (including site(s) of application and pest(s) controlled), Application Methods, Application Rates, Frequency of Application, and Product Formulation Percentages. Also indicate whether the new chemical will be used in combination with other registered pesticides.

7. Brief Overview Summary of the Health, Ecological and Environmental Fate Effects.

8. Tier 1 statement stating which of the four FQPA criteria are being met by this application.

9. Reduced-Risk Statement, articulating the specific factors that lead the applicant to the conclusion that the active ingredient offers the opportunity for risk reduction.

10. Data Matrix, providing tabular information on all data available for the active ingredient. The table should include the guideline reference number, the study title, MRID number (if available), outcome of the

Agency's evaluation (i.e., in review, acceptable, supplemental, data waived, etc.), and date of the Agency's review (if applicable).

B. Human Health. Clearly identify the portion of the rationale which addresses the potential effects of the active ingredient on human health. When specifying the dose levels used in the toxicity studies, present the no-observable-effects level (NOEL) and the lowest-observable-effects level (LOEL). Doses need to be specified in terms of mg/kg/day. Also, describe qualitatively and quantitatively the array of effects at all dose levels tested. In the format described in Part IX of this PR Notice, address each of the following aspects of the active ingredient and its use:

1. Acute Toxicity of the active ingredient and the formulations. Provide the toxicity category for each of the acute toxicity studies conducted on the active ingredient and the formulated products.

2. Reproductive, Developmental, Mutagenic and Neurotoxic Properties of the active ingredient.

3. Oncogenic and Other Subchronic and Chronic Effects of the active ingredient.

4. Toxicity of Mammalian and Plant Metabolites.

C. Environmental Fate and Effects. Clearly identify the portion of the rationale which addresses the potential ecological effects of the active ingredient and its environmental fate. The discussion should also address potential environmental degradates or metabolites of the active ingredient. Address each of the following aspects of the active ingredients and its use:

1. Mammalian Acute Toxicity

2. Avian Acute and Subacute Toxicity

3. Avian Reproductive Toxicity

4. Fish Acute and Chronic Toxicity

5. Aquatic Invertebrate Toxicity

6. Honeybee Acute Contact Toxicity

7. Effects on Terrestrial Plant Growth

8. Effects on Aquatic Plant Growth

9. Potential Exposure to Non-target Organisms

10. Environmental Persistence (Soil and Water)

11. Mobility in Soil and Water

12. Transport in Air (Spray Drift and Volatility)

13. Bioaccumulation as Indicated by the Octanol/Water Partition Coefficient

D. Other Hazards. Clearly identify the portion of the rationale which addresses other potential human health and environmental hazards produced by the following:

1. Potential to Deplete Stratospheric Ozone thus increasing ultraviolet radiation.

2. Potential to Present a Hazard through Storage, Transportation, Mixing, Use or Disposal based on its physical or chemical characteristics:

   a. stability
   b. flammability
   c. corrosion characteristics
   d. explodability
   e. oxidizing or reducing action
   f. storage stability

3. Potential to Affect Endangered and/or Threatened Plant and Animal Species as designated under the Endangered Species Act.

E. Risk Discussion. Clearly identify the portion of the rationale which addresses the following items:

1. Discuss the information which supports the claims that the active ingredient presents reduced toxicity, reduced exposure to humans or non-target organisms, and/or reduced environmental burden. When discussing the ecological levels of concern (LOCs), present the methods used to derive them and provide interpretations of what the LOCs mean.

2. Where alternative, registered pesticides or pest control practices exist, make a quantitative and/or qualitative comparison between the risks posed by the active ingredient under consideration and all the other

pesticides commonly used, and/or the other current pest control practices.

3. The comparisons with alternative technology should also include biological pesticides as well as cultural and mechanical pest management practices.

F. Pest Resistance and Management. Clearly identify the portion of the rationale which addresses the following items:

1. Describe how the active ingredient addresses the development of pest resistance, either to the active ingredient itself or to existing pesticides registered for the same use.

2. Discuss the suitability of the active ingredient for use in, or encouraging the adoption of, Integrated Pest Management (IPM) programs. This discussion should include information on the effects of the pesticide on natural predators, parasites and pathogens of each target pest, if such information is known. The degree of risk and/or usage reduction to be achieved by the IPM program must also be addressed.

G. Comparative Performance Data (efficacy data). These data are important to assure that risk reduction has a reasonable opportunity to be accomplished by adoption of the new pesticide by growers.

1. It is desirable to have summaries of comparative performance data in which the performance of the candidate pesticide is compared to that of alternative control measures under actual-use or simulated actual-use conditions.

2. Summaries of the available efficacy data if comparative performance data are not available.

Summaries should include statistical analysis of significant differences between the new pesticide and the commonly used alternatives. Summaries should also include experimental methodologies such as application rates, application intervals, pest pressure, weather conditions, varieties of the crop used, etc. Unfavorable results must be included. Efficacy experiments performed under substantially different conditions should not be combined (examples include differences in pest pressure, geography, strain/race of pest and weather). Guidance for this requirement can be obtained from standardized published tests such "Fungicide and Nematicide Tests," "Insecticide and Acaricide Tests" and methods section sections of juried professional journals.

H. Other Information. Submission of the following additional information will assist the Agency in making its decision on the active ingredient:

1. A copy of the proposed product label(s).

The Agency will consider all of these criteria using a weight-of-evidence approach.

VIII. GUIDELINES FOR FQPA RATIONALE FOR REDUCED RISK PESTICIDES

Reduced-risk submissions should also provide a rationale that explains how this registration action complies with the requirements of FQPA. Such rationale should follow guidance provided in Appendix A of PR Notice 97-1 (January 31, 1997). Such rationale should address at a minimum aggregate risk, special sensitivities, endocrine effects and potential common mechanisms of toxicity with other registered pesticides. Appendix A is provided as an attachment to this notice.

IX. FORMATTING AND SUBMITTAL PROCEDURES FOR REDUCED-RISK PESTICIDES

Formatting (A) and submittal (B) procedures for Reduced-Risk Rationales are provided below. These procedures will enable EPA to easily identify the application for priority consideration. Also, applicants should note that it is unlawful to falsify any portion of an application. FIFRA Sections 12(a) (2)(M), 12(a)(2)(R) and 18 U.S.C. Section 1001 make such actions unlawful and can result in civil or criminal penalties. The Agency will not consider an application under the Voluntary Reduced-Risk Pesticide Initiative if the applicant does not follow these procedures.

A. Format. The reduced-risk rationale document must include the following elements in the order indicated: Title Page, Statement or Supplemental Statement of Data Confidentiality Claims, Cover Sheet to Confidential Attachment and Confidential Business Information (CBI) Reduced-Risk Attachment. Any supporting data must comply with PR Notice 86-5 requirements.

The Reduced-Risk Rationale must be bound as a separate entity and consecutively paginated beginning with the title page as page 1. The total number of pages must be represented on the title page. Do not include CBI on the title page. On the title page, include titles and author(s).

B. Submitting a Reduced-Risk Rationale Registration Application. The Reduced-Risk Rationale should accompany the registration application and supporting data packages. This PR Notice does not supersede established submittal procedures as addressed in PR Notice 91-5; rather, this PR Notice provides additional guidance for submitting the reduced-risk rationale. OPP uses distribution codes to facilitate the delivery of registration and other

submissions within the program. When preparing your submission to mail or deliver to OPP, direct your submission to the Document Processing Desk and including the following distribution code: **REDUCED-RISK APPL.**

The submission delivered via the U.S. Postal Service should be directed to OPP using the following address:

Document Processing Desk (**REDUCED-RISK APPL.**)
Office of Pesticide Programs (7504C)
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460-0001

Submissions via personal or courier delivery should be directed to the Document Processing Desk between the hours of 8:00 a.m. and 4:00 p.m., Monday through Friday, excluding federal holidays. OPP's Document Processing Desk is located at the following address:

Office of Pesticide Programs
Document Processing Desk (**REDUCED-RISK APPL.**)
Room 266A, Crystal Mall 2
1921 Jefferson Davis Highway
Arlington, VA 22202

C. Rebuttals may be submitted to Rick Keigwin, Registration Division (7505C), U.S. Environmental Protection Agency, 401 M Street, S.W., Washington, DC 20460.

X. GUIDELINES FOR EXPEDITED REVIEW OF NON-FAST-TRACK NEW FORMULATIONS FOR CURRENTLY REGISTERED CONVENTIONAL PESTICIDES

Some new, non-fast-track, formulations and amendments to currently registered conventional pesticide products could result in reduced risk. To qualify, an application for expedited review under this section must first demonstrate that it meets one or more of the step 1 criteria listed in section VI.A of this notice. Secondly, the registrant must demonstrate that the new formulation, when compared with all of the existing formulation(s) for the active ingredient, results in significant risk reduction. Examples of risk reduction that would most likely qualify for expedited review include new formulations that result in (a) at least a 35% reduction in the amount of active ingredient applied, (b) at least a ten fold reduction in risks to mixers, loaders and applicators, (c) at least a 50% reduction in the product's potential to leach into groundwater or run off into surface water or (d) a significant reduction in risk to non-target species. Actions that are accepted will qualify for expedited review but will not be classified as reduced risk.

The process for submission of a non-fast-track formulation or new end-use product differs from the new active ingredient/new uses procedures. For consideration of a non-fast-track new formulation/end-use product, the registrant shall make a submission to the Product Manager with documented rationale for consideration of expedited review. The Product Manager will review the request and determine if the submission qualifies for expedited review. Consultation with other Product Managers or Branch Chiefs in Registration Division may be necessary. The Product Manager will notify the applicant of the expedited review status within 30 days. If denied expedited review status, there will be one opportunity for rebuttal; the submitter has four weeks to resubmit their rebuttal to the PM. Finally, if the applicant holds the registrations for the old formulations that this new formulation will replace, a request for cancellation of the old formulations is also required. This cancellation request will not be processed until a registration is issued on the new formulation.

XI. BIOLOGICAL PESTICIDES

A. Background. In November, 1994, EPA established a pilot division, the Biopesticides and Pollution Prevention Division (BPPD), with part of its mission to expedite the registration and reregistration of biological pesticides (biopesticides). Biopesticides are any of the following: (1) naturally occurring or genetically altered microorganisms, (2) plant-pesticides (pesticidal substances produced in a plant and the genetic material necessary for the production of those substances), or (3) biochemical pesticides. In addition, BPPD does review the registration submissions for some other pesticidal substances which warrant a reduced data set as described below in Part C.

BPPD is now a permanent part of the Office of Pesticide Programs. To date, BPPD has been successful at expediting the registration of biological pesticides. Since the Division was established in the fall of 1994, 37 new biological pesticides have been registered including the first plant-pesticide products. New biopesticide active ingredients are typically registered in less than 11 months which is substantially less time than the average review time for conventional pesticides.

B. Priority for Review in BPPD. EPA believes that biological pesticides generally pose less risk than most conventional pesticides. Therefore, EPA established BPPD to provide an expedited review to all biological pesticide products. BPPD's priority of actions is based upon the order submissions are received rather than a comparison of risk among the biopesticides. When a particular pesticide registrant requests that a certain one of its submissions receives top priority amongst that company's other biological actions, BPPD honors the requests. Also, if a biopesticide would replace the use of a hazardous pesticide requested for an emergency exemption under FIFRA Section 18, BPPD would make a case-by-case determination on whether to further expedite the regulatory decision.

C. Characteristics of Biopesticides

1. Microbial Pesticides. Microbial pesticides contain a bacterium, fungus, virus, protozoan or alga as the active ingredient. Approximately 50 microbial pesticide active ingredients are registered by EPA. The most widely known of these are varieties of the bacterium, *Bacillus thuringensis* or Bt, which can control certain moths, beetles, and mosquitoes. Data requirements for microbial pesticides are found in 40 CFR 158.740. BPPD encourages potential registrants to contact the Division for a preregistration submission meeting to discuss these data requirements, and the scientific rationales for study waivers.

2. Plant-Pesticides. In November of 1994, EPA published a proposed rule for regulation of plant-pesticides. In that document, EPA encouraged potential registrants to follow the proposed rule until the final rule is published. To date, seven plant-pesticide registrations have been issued. Once the final rule is published, EPA will propose guidelines for registration of plant-pesticides which will be incorporated into 40 CFR Part 158. The guidelines will be open to public comments and appropriate public meetings will be held prior to final guidelines being issued. In the meantime, potential registrants should work closely with BPPD to determine the data requirements for their products.

3. Biochemical Pesticides. Biochemical pesticides are distinguished from conventional chemical pesticides by their nontoxic mode of action toward target organisms (usually species specific), e.g. growth regulation or mating disruption, and by the natural occurrence of the pesticidal substance. In contrast, conventional pesticides generally are toxic and may affect a wider range of target species. Biochemical pesticides generally fall into distinct biologically functional classes: Semiochemicals (chemicals emitted by a plant or animal that modify the behavior of receptor organisms of similar or different species), hormones, natural plant regulators, natural insect growth regulators, and enzymes. In many instances, biochemical pesticides may be synthesized rather than isolated from nature. In order for synthesized pesticides to be considered as biochemical pesticides, they must be demonstrated to be structurally similar and functionally identical to a naturally occurring biochemical pesticide.

Although there are no strict criteria for the definition of biochemical pesticides, most biochemical pesticides are applied at very low rates, are highly volatile, or are applied in bait, trap, or "encapsulated" formulations, thus resulting in less exposure (and less likelihood of adverse effects to humans and the environment than from use of most conventional pesticides). In keeping with their unique properties, biochemical pesticides have been assigned a set of data requirements which are organized in a tiered testing scheme to ensure, to the greatest extent possible, that only the minimum data sufficient to make scientifically sound regulatory decisions will be required. The data requirements are outlined in 40 CFR Part 158.690.

4. Pesticides Which Warrant Reduced Data Requirements. The Agency recognizes that many naturally occurring pesticidal chemicals may be highly toxic to their target organisms and does not intend to include these as biochemical pesticides. BPPD has elected to review certain of these naturally occurring pesticides that may operate via a toxic

mode of action toward target organisms, but which *a priori* also would be candidates for an initial tiered data set, as required for biochemical pesticides. These "biochemical-like" pesticides have not yet been formally classified into a subcategory of pesticides for nomenclature purposes. These pesticides usually have uncomplicated structures and are commonly present in the environment or the human diet at significant levels or have been widely used for non-pesticidal purposes. Thus, any clinical or nontarget effects are very likely to have been noticed and should be well documented. BPPD has found that potential registrants for these products generally follow the same data requirements as the biochemicals, but a preregistration meeting with the Division is highly recommended before extensive testing and before formal submission of an application.

D. Guidelines for Classification as a Biochemical or a "Biochemical-like" Pesticide to be Reviewed by BPPD. On request, the Biopesticides and Pollution Prevention Division (BPPD) will evaluate products on an individual basis to classify them as biochemical pesticides, pesticides warranting reduced data requirements ("biochemical-like"), or conventional chemical pesticides.

BPPD has formed a Biochemical Classification Committee to evaluate written requests for classifying products proposed for BPPD review as biochemicals and similar products. A classification request should include information to support the natural occurrence of the chemical and information bearing on its mode of action toward the target pest. Additional information to support low toxicity or low exposure levels may be useful if available. This could include GRAS (generally regarded as safe) status (please cite the listing number) or information on application rates and/or degradation rates. Published studies or private data should be attached if the supporting information is not commonly known or obvious.

E. Evaluation Standards

1. Natural Occurrence. Naturally occurring substances may be inorganic or organic. As noted above, if the chemical is not naturally occurring, information must be provided showing that it is structurally similar and functionally identical to a naturally occurring substance. The Biochemical Classification Committee recognizes that "natural occurrence" may technically include substances that occur at very low levels in the environment, but in such amounts or locations that humans and/or nontarget organisms have not been exposed to significant levels of these chemicals. The committee may decide that these substances are not biochemical pesticides if there is any indication that natural exposure levels are insufficient to indicate potential effects from the expected product exposure.

2. Nontoxic Mode of Action. A nontoxic mode of action is one that does not kill the target pest. The most obvious are repellents and attractants. The committee has also included in the nontoxic mode of action category, those chemicals that may be lethal to the target, but operate via a physical mode of action to control the target pest. For example, certain oils and/or sticky substances can kill insects by clogging their respiratory spiracles and

trachea, but such substances are not likely to have adverse effects on non-target organisms or humans. Desiccants also are considered as acting via a nontoxic mode of action. Plant growth regulators are usually considered to have a nontoxic mode of action; however, some plant growth regulators may act as herbicides at higher application rates. Thus, higher application rates may result in additional data requirements (as required for conventional chemical herbicides) or reclassification as a conventional chemical pesticide.

F. Formatting and Submittal of Request for Biochemical Classification. The classification request should be in the form of a letter and should be sent directly to the Biopesticides and Pollution Prevention Division (7511W), Office of Pesticide Programs, US Environmental Protection Agency, 401 M St SW, Washington, DC 20460. It should be labeled "Attn.: Biochemical Classification Committee."

G. EPA Response to Request for Biochemical Classification. Submissions for classification are reviewed by a team of scientists from several divisions within OPP. The recommendations of the Committee are brought to management for approval. Decisions can include classification as a biochemical, classification as a "biochemical-like" substance that warrants reduced data requirements, but is not a biochemical, or classification as a conventional pesticide. The potential registrant is informed by letter of the decision. Because these are preapplication requests for classification, the information submitted and the results may, upon request, be treated as confidential business information.

H. Rebuttals to Denials for Biochemical Classification. In some cases, inadequate information is supplied so that a Committee recommendation cannot be made. In these cases the potential registrant is asked to submit additional information. If a potential registrant disagrees with classification as a conventional pesticide (essentially a denial of classification as a biochemical), a rebuttal can be submitted to the Biochemical Classification Committee for reconsideration.

XII. FOR FURTHER INFORMATION

For further information on reduced-risk submissions for conventional pesticides, contact Peter Caulkins, Associate Director, Registration Division at (703)305-6550. For further information on antimicrobial pesticides, contact Bill Jordan, Associate Director, Antimicrobials Division at (703)308-6411. For further information on microbial and plant-pesticides, contact Phil Hutton, Chief, Microbial Pesticides Branch, BPPD at (703) 308-8260 and for biochemicals, contact Roy Sjoblad, Chief, Biochemical Pesticides Branch, BPPD at (703) 308-8269.

Daniel M. Barolo, Director
Office of Pesticide Programs

APPENDIX A

CONTENT OF SUPPLEMENTAL INFORMATION

As indicated at the beginning of the PR Notice, registrants, applicants and petitioners are not currently required to submit any additional information. Nevertheless, since the new statute requires the Agency to consider additional information in order to make the necessary decisions, EPA recognizes that many registrants, applicants and petitioners may wish to provide the supplemental information to the Agency even without a requirement to do so. For those registrants, applicants or petitioners who wish to supplement their original submissions with additional information, this Appendix describes what information the Agency would consider helpful additions for its review.[1]

All tolerances or tolerance exemptions and associated registration actions under FIFRA section 3 or reregistration actions under FIFRA section 4, whether pending or future, will need to comply with the new safety standard of section 408(b)(2) of the Federal Food, Drug and Cosmetic Act. In addition, because EPA intends to apply a similar standard to actions involving non-food use pesticides that may pose significant non-dietary risks to infants and children, all registration and reregistration actions also will need to comply with this standard with respect to the Agency's consideration of infants and children exposure to the pesticide.

In preparing a package to be submitted, those seeking a registration, reregistration, tolerance, or an exemption from the requirement of a tolerance for a food use pesticide, or a registration or reregistration of a non-food use pesticide that may result in significant exposure to children, may need to provide additional information and/or materials to address adequately the factors and specific questions contained here. Those who wish to submit additional information should keep in mind that the Agency will consider each factor listed below (and perhaps others as Agency policies are developed) in addition to any data and information already required. In addition, it is important to note that the information identified here may not be definitive in all cases. Additional information or more detailed information may be needed in individual cases. If a registrant, applicant, or petitioner can identify additional information that would assist the Agency in addressing the FQPA provisions, EPA welcomes

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[1] An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it either displays a currently valid OMB control number or is imposed on the person by statute (5 CFR 1320.6(a) & (e)). The collection of information relating to the registration, reregistration, and tolerance programs have are approved under OMB Control Numbers 2070-0024 (expires: 6/30/99); 2070-0032 (expires: 5/3/98); 2070-0040 (expires: 11/30/99); 2070-0060 (expires: 5/31/98); 2070-0122 (expires: 11/30/97); 2070-0107 (expires: 7/31/99). If you should have any comments on the collection activities, please send them to the Director, OPPE Regulatory Information Division, U.S. Environmental Protection Agency (Mailcode 2137), 401 M St., S.W., Washington, D.C. 20460. Include the OMB control number in any correspondence. Note that this address is ONLY for comments on the collection activity. Do not submit your information to this address.

such information. Although the submission of this information is not currently required by the regulations, if such information is not submitted, the Agency must rely on previously submitted data, if applicable, or on broad or default assumptions when considering the factors listed. As a result, favorable action on an application, petition, or reregistration decision may be significantly delayed or precluded altogether.

It would be helpful for any submitted documentation to contain a discussion of each of the following factors as it relates to the pesticide and proposed tolerance or tolerance exemption. If information on any factor is not known, that fact, along with an explanation, should be noted in the rationale. It is important to note that EPA does not expect the registrant, applicant, or petitioner at this time to perform any additional testing to derive the data necessary to develop its rationales. However, if it has in its possession data from preliminary reports of ongoing studies, articles from published literature, unpublished report information, previously unsubmitted studies, or supplemental data that are otherwise pertinent to the Agency's concerns, the party is encouraged to submit them. Likewise, if a registrant, applicant, or petitioner believes that a factor is not applicable to its product, a discussion as to why this view is held should also be included. The Agency will consider all relevant factors in determining an application's completeness and in setting priorities for review.

Based on the new safety standard, EPA will need the following additional information in order to make appropriate regulatory decisions: (For details on each factor, please refer to the explanations below in parts A and B.)

1. An informative summary of the petition or application, including a summary of the supporting data, information, accompanying rationales, and a statement providing permission to publish such summary, and

2. Information and discussion pertaining to a specific safety determination for infants and children including their special susceptibilities and exposure patterns to the particular pesticide.

A. Food Use Pesticides: Registration and Reregistration Actions, Experimental Use Permits, Tolerance (or Exemption) Petitions and Reassessments

In the format described in Appendix C of this PR Notice, address each of the following with respect to the pesticide and its use(s):

Special Sensitivities

a) Chronic Endpoints

For a chemical pesticide: Discuss and/or provide evidence as to whether or not the current Reference Dose (RfD) is sufficient to adequately protect infants and children. Discuss and/or provide evidence as to whether or not infants and children are more

susceptible to the chemical. If you believe that an additional safety factor of 10X, to take into account potential pre- and post-natal toxicity to infants and children is not necessary, provide evidence to support the additional safety factor, if any, you believe to be more appropriate. Please bear in mind that the Agency may accept a different margin of safety only if, based on reliable data, EPA concludes that the margin will be safe for infants and children.

For a biochemical pesticide:[2] Does the toxicity testing indicate that the establishment of an RfD is warranted? If so, then discuss whether or not the RfD is sufficient to adequately protect infants and children. Discuss and/or provide evidence as to whether or not infants and children are more susceptible to the biochemical pesticide.

For a microbial pesticide:[3] Discuss the potential for chronic dietary risks for infants and children. Discuss and/or provide evidence as to whether or not infants and children are more susceptible to the microbial pesticide than is the adult population.

b) Acute Endpoints

Discuss the potential for greater acute dietary risk for infants and children. If the chemical or biochemical pesticide demonstrates acute effects, then discuss the endpoint used to perform the assessment including relevance to infants and children and the details as to how the exposure assessment was conducted and whether the estimated risk is within the Agency's levels of concern.

c) Carcinogenic Endpoints

If the chemical or biochemical has been determined to be a carcinogen and has a cancer potency factor (Q_1*), discuss the aggregate excess lifetime cancer risk resulting from exposure to the chemical from residues in food and drinking water (ground and surface water) and from residential and other non-occupational source(s).

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[2] A biochemical is a naturally-occurring compound, or substantially similar to a naturally-occurring compound, with a non-toxic mode of action to the target pest.

[3] Certain subpopulations are more susceptible to certain disease-causing microorganisms; however, these are not the types of microorganisms that are considered for registration or use as microbial pesticides. The Agency has not registered, and does not expect to register a microbial active ingredient that is known to be a common human pathogen. To address the potential risk from microbial pesticides, the Agency requires a battery of acute toxicity/pathogenicity studies in order to perform a risk assessment. If results of the acute exposure studies indicate a toxicity concern, then subchronic or chronic studies are required.

Aggregate Exposure

a) Water

For a chemical or biochemical pesticide: Discuss the potential for the transfer of residues (of both the parent pesticide and any degradates) to drinking water. The discussion should include, but not be limited to, information indicating whether the pesticide is persistent and/or mobile, relevant product chemistry, and any available modeling data.

Has the chemical or any of its degradates been detected in ground water or surface water? Would this chemical or any of its degradates likely pass through primary or secondary drinking water treatment into finished water? Are any States conducting water monitoring programs for this pesticide? If so, data collected by the States and all relevant information should also be included.

For a microbial pesticide: Discuss the potential for the transfer of the microbial pesticide to drinking water. The discussion should include, but not be limited to, information pertaining to the biology of the microorganism, and indicating whether the pesticide is persistent and/or mobile or has the potential for transport in air (spray drift and volatility data). Are any States conducting water monitoring programs for this strain? If so, data collected by the States and all other relevant information should also be included.

b) Non-occupational Exposures

Discuss the potential for significant exposure to the pesticide of children by routes other than dietary. Are there any non-occupational, structural, or residential uses (e.g., pet, swimming pool, lawn and garden, or topical insect repellent)? Is the pesticide used in or around schools, parks, or recreation facilities? Provide all available exposure data. If the pesticide demonstrates acute effects, then discuss the endpoint used to perform the assessment, including relevance to infants and children and the details of how the residential exposure assessment was conducted and whether the estimated risk is within the Agency's levels of concern.

c) Multiple Pathway Assessment

Discuss the chronic and/or acute risk of aggregate exposure via multiple pathways for the general population, and for infants and children. This should include a discussion of all assumptions used and uncertainties. You should also identify, and include in the discussion, any non-pesticidal uses of the chemical (e.g., industrial, pharmaceutical, cosmetic, food additive).

Cumulative Effects

Discuss the mechanism and mode of action of this pesticide. Identify other chemicals that may fall into this category (both pesticide and non-pesticide chemicals). Provide information regarding common mechanisms and modes of action with other chemical substances based on structural similarity, same or similar endpoints, and other relevant criteria. Provide any data and/or evidence illustrating similarities at the cellular/molecular level.

Discuss the appropriateness of combining exposures in this particular case. Where data are not available, discuss appropriateness of using default assumptions and what defaults should be used.

Endocrine Effects[4]

Discuss and provide any evidence relevant to the possibility that the pesticide may have endocrine disrupter effects individually or in combination with another chemical. Include the potential for synergistic effects of your chemical in combination with other chemicals.

Identify any instances of reported (proven or alleged) adverse reproductive or developmental effects to domestic animals or wildlife as a result of exposure to your chemical, or that occurred in an area where the chemical is known to have been used. Provide all information regarding the circumstances, estimated level of exposure, and details of the effect.

Residue Chemistry

Information should include a discussion of compatibility with established Codex Alimentarius Commission Maximum Residue Levels (MRLs), submission of a practical analytical method with an appropriate limit of detection, and a discussion of the potential need for tolerances for processed foods. For tolerance exemption petitions, indicate if the chemical is on the Food and Drug Administration's Generally Recognized As Safe (GRAS) list. A summary of all tolerances and exemptions from tolerance being proposed should also be included.

Benefits Information (For Reregistration Actions Only)

If the information and data submitted indicate that an existing tolerance, reviewed according to the requirements of the new legislation, should be determined to be unsafe (that

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[4] As indicated in section 408(p)(1) & (2), the Agency has 2 years to develop a screening method, with a total of 3 years to implement such a program.

is, to exceed the "reasonable certainty of no harm" standard), the new law allows EPA to consider pesticide benefits information in certain instances. An "eligible pesticide chemical residue" (for which an "eligible tolerance" may be applicable) is defined as a chemical residue for which

1) EPA is unable to identify a level of exposure that will not cause or contribute to a known or anticipated harm to human health (that is, the effect is a non-threshold effect);

2) an appropriate quantitative risk assessment for the lifetime risk of the non-threshold effect has been determined; and

3) if there are also threshold effects associated with the chemical, EPA is able to identify a level at which the residue will not cause any known or anticipated harm to human health and that the level of aggregate exposure is safe.

Registrants who suspect that an existing tolerance for their chemical, which has been classified by the Agency as exhibiting a non-threshold effect, may exceed the new safety standard, and wish the Agency to consider an eligible tolerance for residues of that pesticide, may need to submit the following information:

Conditions Regarding the Use of the Pesticide

Information and/or data indicating that the use of the pesticide chemical that produces the residue protects consumers from adverse health effects that would pose a greater risk than the dietary risk from the residue, OR

Information and/or data showing that the use of the pesticide chemical that produces the residue is necessary to avoid a significant disruption in the domestic production of an adequate, wholesome, and economic food supply.

Conditions Regarding the Risk of a Pesticide

Evidence that the yearly risk associated with the nonthreshold effect from aggregate exposure to the residue is not greater than ten times the yearly risk allowed under the new safety standard, AND

Evidence that the tolerance is limited to ensure that the lifetime risk associated with the nonthreshold effect from aggregate exposure to the residue is not greater than twice the lifetime risk allowed under the new safety standard.

It is important to note that the above information does not supersede any existing benefits requirements under FIFRA, such as public health pests and benefits data necessary for a public interest finding under FIFRA section (3)(c)(7).

B. Non-Food Use Pesticides: Registration or Reregistration Actions

In the format described in Appendix C of this PR Notice, address each of the following with respect to the pesticide and its use(s):

Potential for Exposure to Children

Describe the use pattern of your chemical. If you believe that its use(s) would not potentially result in significant exposure to infants and children, provide a discussion and rationale as to why this view is held. For chemicals that appear not to result in a significant exposure to infants and children, no additional information is needed.

If you believe that the use of your chemical may result in significant children's exposure, the following factors may need to be addressed:

Special Sensitivities

Discuss and/or provide evidence as to whether or not infants and children are more susceptible to the chemical than adults.

Discuss the potential for greater acute and/or chronic risk for infants and children. If the pesticide demonstrates toxic effects, then discuss the endpoint used to perform the assessment including relevance to infants and children and the details as to how the exposure assessment was conducted and whether the estimated risk is within the Agency's levels of concern.

Aggregate Exposure

Discuss the potential for the transfer of residues of both the parent chemical and any degradates or of the microbial pesticide to drinking water. For chemical pesticides, the discussion should include, but not be limited to, information indicating whether the pesticide is persistent and/or mobile, the potential for transport in air (spray drift and volatility data), and any available modeling data. For microbial pesticides, the discussion should instead include information pertaining to the biology of the microorganism and indicate whether the pesticide is persistent and/or mobile.

Has the chemical or any of its degradates been detected in ground water or surface water? Would this chemical or any of its degradates likely pass through primary or secondary drinking water treatment into finished water? Are any States conducting

water monitoring programs for this pesticide? If so, data collected by the States and all relevant information should also be included.

Discuss the potential for significant exposure to the chemical of children by non-dietary routes. Are there non-occupational, structural, or residential uses (e.g., pet, swimming pool, lawn and garden, or topical insect repellents)? Is the pesticide used in or around schools, parks, or recreation facilities? Provide all available exposure data.

Discuss the chronic and/or acute risk of aggregate exposure via multiple pathways for the general population, infants and children should include a discussion of all assumptions used and uncertainties.

Identify other non-pesticidal uses of the chemical (e.g., industrial, pharmaceutical, cosmetic, food additive).

Cumulative Effects

Discuss the mechanism and mode of action of this pesticide. Identify other chemicals that may fall into this category (both pesticide and non-pesticide chemicals). Provide information regarding common mechanisms and modes of action with other chemical substances based on structural similarity, same or similar endpoints, and other relevant criteria. Provide any data and/or evidence illustrating similarities at the cellular/molecular level.

Discuss the appropriateness of combining exposures in this particular case. Where data are not available, discuss appropriateness of using default assumptions and what defaults should be used.

Endocrine Effects

Discuss and provide any evidence relevant to the possibility that the chemical may have endocrine disrupter effects individually or in combination with another chemical. Include the potential for synergistic effects of your chemical in combination with other chemicals and whether or not your chemical could act as a catalyst for another hormone-disrupting chemical.

Identify any instances of reported (proven or otherwise) adverse reproductive or developmental effects to domestic animals or wildlife as a result of exposure to your chemical, or that occurred in an area where the chemical is known to has been used. Provide all information regarding the circumstances, estimated level of exposure, and details of the effect.

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Environmental Protection Agency
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