



September 7, 2005

Public Information and Records Integrity Branch (PIRIB) (7502C)
Office of Pesticide Programs (OPP)
Environmental Protection Agency
1200 Pennsylvania Ave, NW
Washington, DC 20460-0001

Re: Proposed Revisions to Pesticide Data Requirements for Conventional Chemicals. 70 FR 12275. March 11, 2005. EPA Docket Number OPP-2004-0387

Ladies and Gentlemen:

CropLife America (CLA) is pleased to comment on the proposed revisions to 40 CFR Part 158 ("proposed regulation"). We commend EPA for its efforts to bring this lengthy process to fruition, and look forward to a final rule that will bring greater predictability to pesticide registrations and improve the pesticide regulatory process. We gratefully acknowledge the input of a large group of experts from numerous technical committees and work groups in compiling these comments. In particular, we thank Greg Leyes of ISK Biosciences for his chairmanship of the Part 158 Comments Team, and Ed Johnson of Technology Sciences Group for his technical coordination of the process.

CLA and other stakeholders need additional information on a number of issues and topics in order to provide complete and meaningful comments to EPA on the proposed regulation. We, along with others, have requested that EPA establish an open stakeholder dialog to resolve these issues. We are disappointed that the Agency has so far declined these requests. The long, drawn-out process of formal written proposals, followed by formal written comments, then more proposals, and so on can be dramatically and efficiently compressed by an open stakeholder dialog, resulting in a much better final regulation. We will continue to pursue this end. The following are specific issues that should be addressed in such a dialog. We believe other stakeholders have identified additional issues that should be accommodated in a dialog process.

1. Economic analysis. It is not possible to comment on the economic analysis since there are too many unknowns at this time. For example, it is not clear at present how Part 158 will be applied to existing product registrations. Study costs cannot be estimated in the absence of promulgated guidelines in many areas.
2. ILSI Agricultural Chemical Safety Assessment. This project, well underway, promises to provide current scientific approaches to assessing the safety of agricultural chemicals while minimizing the use of animals in testing. Its conclusions could greatly improve the provisions of Part 158. EPA should fully consider this information before finalizing Part 158 proposals.

3. EPA proposes to remove the Use Pattern Index, Appendix A of the current Part 158 and instead make it available as a guideline. This Index provides key information to industry in determining data requirements and for assessing the economic impact of proposed changes in Part 158. It must be the subject of notice and comment on changes and remain in the rule itself.
4. The sections dealing with the Formulators Exemption and Minor Uses are essential to spelling out the effects of Part 158 in those two areas. As such they should be retained in the regulation in close proximity to the data requirements.
5. CBI provisions are essential to the protection of the large investments made by manufacturers to bring a pesticide to market. The proposal made in the proposed Part 158 negates a large measure of protection envisioned in the statutory language.
6. No attempt to harmonize the data requirements with other world areas, such as the European Union, or with the Organization for Economic Cooperation and Development (OECD), of which the United States is a member, seems to have been made.
7. In many instances, the guidelines referenced in the data requirements tables do not exist or have not been validated. The guideline references in Subpart N, Environmental Fate, are not available. In Subpart E, Terrestrial and Aquatic Nontarget Organisms, the guidelines that are referenced have never been finalized by the Agency. Specialized neurotoxicity test guidelines have never undergone interlaboratory validation.
8. The distinction between studies which are normally always performed as part of a study package (designated R) and those that are only conditionally required (CR) seems to have blurred to the point that it is difficult to interpret the Agency's position.
9. Some data requirements, notably those involving endangered species assessments, are ill-defined and provide no guidance on how to satisfy data needs.
10. The proposed rule makes changes to the flagging criteria for reporting potential adverse effects that could significantly increase the burden to registrants.

Part 158 must strike a robust balance between (a) the certainty that registrants need in deciding on data requirements to support applications for new products and to support already registered products and uses; and (b) flexibility needed to accommodate special circumstances, minor crops, and unique risk and exposure scenarios.

We reiterate our position, expressed to the Agency in other forums, that the Part 158 rule must be implemented in coordination with the Registration Review rule (Docket No. OPP-2004-0404), also under review at this time. Part 158 must establish the ground rules for registrants to meet in steering their products through the new Registration Review process.

CLA continues to evaluate this very complex proposed rule. If additional issues arise or we feel that clarification of these comments is in order, we will submit additional comments to the docket.

Sincerely,

A handwritten signature in black ink that reads "Ray S. McAllister". The signature is written in a cursive style with a large, stylized initial "R" and "M".

Ray S. McAllister, Ph.D.
Regulatory Science & Policy Leader

Comments of CropLife America

on

Proposed Revisions to 40 CFR Part 158 Data Requirements for Registration 70 FR 12276; March 11, 2005 Docket No. OPP-2004-0387

September 7, 2005

CropLife America (CLA) is the national trade association representing the developers, manufacturers, formulators and distributors of plant science solutions for agriculture and pest management in the United States. CLA member companies produce, sell and distribute virtually all the crop protection and biotechnology products used by American farmers.

Organization of comments

Following the General comments, additional comments are organized by subject matter sections according to the various Subparts in the proposed rule. Each section includes comments on the Subpart from the actual proposed rule, as well as on the related background and explanatory material in the Preamble.

Throughout the comments, page numbers refer to the Federal Register publication of the proposed rule (70 FR 12275; 3/11/2005), unless otherwise indicated. Lower-case letters appended to FR page numbers divide refer to the top and bottom of text columns 1 through 3, in sequential order. Individual study requirements are identified by the Guideline numbers from the OPPTS Harmonized Guidelines (see <http://www.epa.gov/opptsfrs/home/guidelin.htm>), as listed in the various data requirements tables. Comments about the Preamble refer to the “Units” organization of that section, e.g., Unit XIX.B.2. Comments about the actual proposed rule refer to the Sections it is subdivided into, e.g. §158.500(c). Comments about test notes for each data requirements table refer to specific test note numbers.

General Comments, including the Preamble and Subpart A

1. CLA appreciates the opportunity to comment on the proposed revisions to 40 CFR 158. However, we are disappointed that EPA has declined requests to hold an open stakeholder dialog to refine the details of the proposed rule. The proposed rule is complex, contains some controversial proposals, and could benefit by both dialogue and input from ongoing activities such as the ILSI Health and Environmental Sciences Institute (HESI) project, “Developing Strategies for Agricultural Safety Evaluation.” It is difficult to understand the rush to finalize these changes in two respects. First, most of the proposed changes are “codification” of data requirements that have already been implemented. Second, the Agency has taken 21 years since the initial promulgation of Part 158 and 11 years from the last proposal to reach this

point. A few more months to accommodate a stakeholder dialog could really improve the product without harm or hardship to anyone.

2. Over the years EPA has stated various goals of the pesticide program, against which these proposed Part 158 changes must be assessed. For example:
 - a. Reduce number of animals tested: It appears that these guidelines can do nothing but increase the numbers of animals used in tests.
 - b. Increase efficiency and transparency of the registration program: Adding tests of dubious value (which we will note in specific comments) does not add to the efficiency of the program nor improve the protection of health and the environment. Providing ambiguous rationales for tests and criteria for CR studies does not promote transparency.
 - c. Harmonization: EPA has recently announced its intent to adopt the OECD study templates and the OECD Vision for worksharing with other pesticide regulatory authorities worldwide. There is no indication that that commitment has been considered in the proposed regulation. Also, the comments submitted by the European Commission indicate a wide range of differences with the proposed Part 158. We note that comments of the European Commission complain about the incompatibility of the proposal with EU standards. (See OPP-2004-0387-0051 and OPP-2004-0387-0052)
 - d. There is no indication that consideration of the requirements of our important trading partners were incorporated in the development of the proposal. This situation can only hamper the concept of a single dossier, acceptable in multiple nations.
 - e. Encourage safer pesticides: Many of the new “safer pesticides” do not have the broad markets of the older broad-scale products. The addition of new requirements and change of many requirements from conditionally required to required increase the cost of registration of these products and can serve as an obstacle to their commercialization.
3. In CLA’s view, Part 158 should have:
 - a. A tight set of required studies which are almost always required for registration, subject to well-reasoned waiver requests.
 - b. A well-defined set of conditionally required studies, with a clear statement of the conditions under which they will be required. We believe that EPA has actually blurred the definitions between R and CR, reducing the certainty for the applicant and imposing additional time and cost burdens. More detailed comments are included on this point. OPP should make clear in the final rule a process for how conditional requirements will be decided in each specific circumstance. Given the broad battery of guidelines proposed that are as conditional requirements, a transparent peer-review process should be established. The role in this process of various officials and regulatory mechanisms should be made clear: conditional registrations, data call-ins, various risk managers, technical review committees, registrant appeals, etc. EPA must clearly, specifically, and formally articulated in writing when CR studies are required for each product, as these requests or requirements will form the basis for any future data compensation claims.

- c. No requirement for studies that are not specifically linked to a risk assessment supporting a registration action; no studies that do not have validated test methods; and no studies that require the applicant to develop research methods or conduct research types of studies.
- d. No studies that lack formally approved guidelines or do not fill a clearly defined regulatory need.

CLA's analysis of the proposal thus far indicates that these criteria are not yet met by the proposed rule.

- 4. The proposed rule removes §158.50 dealing with Formulator's Exemption to Part 152, although no corresponding addition to Part 152 has been proposed. The Formulators Exemption provisions are very important to understanding the requirements imposed on formulators and should be in close proximity to the data requirements. For example, the proposed rule now requires both the TGAI and the EP as test materials for acute testing. The EP formulator needs to understand if he is required to provide acute data for the TGAI. Such a change might open up data compensation or additional testing costs which were never envisioned under the Formulators Exemption. CLA requests that the Agency retain the Formulators Exemption and clarify what is and is not required under the Formulators Exemption.
- 5. The proposed rule deletes the Minor Use section (§158.60) as unnecessary. Minor Use provisions are very important to the agricultural community and allow expanding valuable uses in these minor markets by industry and IR-4. EPA states that the protections exist outside the regulations. Nevertheless, the minor use policy should be reiterated clearly in the regulation so that data requirements clearly comply with the policy.

6. **Confidential Business Information**

Information Pertaining to Unregistered Pesticides

The Preamble states that studies on unregistered pesticides (for which an application is still pending) will "seldom" meet the criteria for business confidentiality. The Agency notes that in order for the public to be able to comment on proposed registrations and tolerances, the public should have access to sufficient information to evaluate the risks and benefits of the product. We believe that the Agency's suggestion that studies on unregistered pesticides would not meet the criteria for confidentiality is incorrect. Moreover, it is not necessary to classify such studies as non-confidential in order to foster public participation in the approval process.

The studies supporting an application for a new food-use pesticide registration typically cost in excess of \$10 million, and are part of a total investment in the pesticide of several times that amount. These studies have always been considered by manufacturers to have great competitive value and to be highly confidential, and their confidentiality is carefully guarded. Part of the reason for this is that information in the studies can provide leads to competitors for inventing structurally-related compounds, for making marketing decisions (in light of potential regulatory issues and the timing of the entry of new products), and for deciding

where to best invest research dollars. Thus, it is incorrect for EPA to say that such a study “is valuable only to the extent that it can be used for registration/tolerance purposes.” 70 FR. 12285. There are many other ways in which these studies could have value if they were available to competitors.

Moreover, it is not true that the competitive injury from disclosure of the studies can be remedied by data compensation. Data compensation typically only becomes a factor many years after the product is registered, when firms seeking to market generic versions of the same pesticide apply for registration. However, as noted above, the information in the studies can be of competitive value at the “front end” of the registration process, when competitors are making product development and marketing decisions. The prospect of possibly receiving an undetermined amount of data compensation 15 years in the future can not ameliorate the harm done by leaking valuable leads to competitors that could undercut the value of an expensive new product.

Nor is FIFRA §10(g) sufficient to prevent competitive harm from occurring. Section 10(g) does not apply to U.S. manufacturers. There has been a surge in recent years of new domestic pesticide registrants whose affiliations are unknown and deliberately kept secret. EPA has taken the position that it is not the business of the Agency to question the affiliations or bona fides of applicants. From the vantage point of CLA members, the disclosure of information of high competitive value, such as studies on products under EPA review, to domestic firms has the potential to cause great competitive injury and is of major concern.

It is also not an answer for EPA to say that there is no harm because “competitors will eventually be able to get access to the information.” A product may be under review for a year or longer, and shielding the information from a competitor during that review period may indeed be of considerable competitive value. The Agency should not be prejudging the outcome of inquiries into the competitive consequences of disclosure of studies pending EPA review, and should approach such issues with an open mind and decide them on a case-by-case basis.

With respect to the matter of public comment on a pending application, there are certainly mechanisms for providing interested persons with sufficient information on which to make informed comments, short of actual disclosure of the full studies. [Interested persons can be provided with DERs, study summaries or EPA risk assessments, which generally provide all of the basic data that would be needed for meaningful participation.] However, it is not necessary to destroy the confidentiality and competitive value of the studies in order to satisfy the objective of facilitating public involvement in the approval process.

Disclosure of Data to Multinational Entities

CLA strongly disagrees with EPA’s standard for determining whether information is subject to the restrictions on disclosure contained in FIFRA § 10(g). EPA’s proposed interpretation

is facially inconsistent with the statutory language and would eviscerate the intended protection.

Under EPA's interpretation, a study submitted by a registrant can be disclosed to foreign and multinational pesticide producers, as long as it does not consist of the "complete" report. That standard would allow disclosure if the report was missing a single sentence, word, or innocuous paragraph, and thus was not the "complete" report.

That is not the standard adopted by Congress. The language used in the statute states that EPA may not disclose "information" submitted by a registrant. The word "information" is far broader than the term "complete report." "Information" consists of any part of the materials submitted to EPA which conveys meaning, facts or knowledge. All of the subsections of a study report contain "information." Thus, strict compliance with the plain language of the statute prohibits EPA from providing any portion of a study to foreign or multinational producers.

Similarly, EPA's proposal would allow the disclosure of excerpts or restatements of a report, unless they reveal (1) the "full" methodology of the study, and (2) the "complete" results of the study, and (3) "all explanatory information" necessary to understand the methodology or interpret the results. Once again, EPA is distorting the plain language of the act to achieve other objectives. Congress did not prohibit disclosure only if the material encompasses "all explanatory information;" nor did it prohibit disclosure only of material that reveals the full methodology and complete results of a study. Congress prohibited the disclosure of any and all "information submitted" by a registrant. Since some foreign regulatory authorities may accept less than the full study to support generic registrations, EPA's proposal would eliminate the intended protections of the multinational disclosure prohibition. In effect, EPA's proposal would rewrite the statute by allowing the disclosure of all of a registrant's studies and submissions to foreign and multinational producers, as long as some small part from each document was omitted. This is plainly contrary to the statutory language as written. EPA should abandon this attempt to distort the statutory meaning and find ways to accomplish its objectives that respect the congressional language. CLA is not aware that EPA's implementation of FIFRA §10(g) over the last several decades has hampered the functioning of the pesticide program, and we would question the need for such linguistic gymnastics. The adoption of this proposed rule would be certain to be the subject of judicial review.

7. Removal of the Pesticide Use Index (Appendix A.) from Part 158 (Unit VIII.A and §158.100): CLA believes that the definitions of use categories should be established by rule rather than being the subject of guidance that can be modified at any time. It is difficult to determine the actual impact on applicants if the guidance is subject to change without notice and comment. The requirements could change and delay the testing/registration program of the applicant. There are also inconsistencies and redundancies in the use categories that are noted in our specific comments.

8. **Section V.C. How the Proposal will Affect Existing Registrations:** The Agency states that this proposal concerns prospective data requirement for new registrants. There are two issues raised in this area.

The first issue concerns new pesticides in the development pipeline. How will the Agency consider applications for new pesticides that submit studies predicated on the existing Part 158 but submitted after the finalization of the new rule? The proposed rule must clearly spell out a phase-in procedure to deal with this issue. This could involve a time-based phase-in, the granting of conditional registrations, or some other option.

Second, before industry can adequately evaluate the burden of the changes in Part 158, it needs to know how the rule will apply to existing registrations. The Agency cannot justify employing one set of data requirements for new pesticides and another set for already registered pesticides. A policy regarding their applicability to reregistration actions needs to be developed and made available for public comment, as it would have significant impacts on the economic burden associated with the proposed rule changes.

9. **General Provisions of Subpart A:** The Agency makes reference to "part 174". To the best of our knowledge, Part 174 Subpart C - Registration Procedures and Requirements" remains "reserved" in the regulations. Therefore, reference to any of these Subparts is inappropriate since there is no way of knowing the requirements that have been superseded without knowing what the requirements actually are.
10. **Waivers:** The Preamble states that waiver requests submitted as part of an application for registration will be reviewed and a decision issued in the same time line as that for the entire application *as per* FIFRA §33. If the waiver is subsequently rejected, then the timelines for the entire application are ruined. This is a huge disincentive for submitting waiver requests and is inconsistent with the apparent desire of the Agency for increased consultation with registrants. The registrants often must have a decision on a waiver request well in advance of submitting the application, so that the data can be generated if the waiver is not granted.

Subpart B—How to Use Data Table

Use Categories (§158.100)

There are several inconsistencies among the use-pattern category names in the various study requirement charts, as shown below, that need to be resolved. The match between the list on Subpart B and the charts in the other subparts is not always apparent. Some simplification and consolidation of the list should be in order, given the similarity of data requirements among the use pattern categories in the various subparts. A detailed listing of the various uses that belong to each category should clarify the situation, emphasizing the need to put this listing in the rule, where its revision is subject to notice-and-comment rulemaking.

	§158.100(a)	Preamble Unit VIII.A	§158.400	§158.500	§158.700	§158.800	§158.1100	§158.1200	§158.1500
(1)	Terrestrial food crop	terrestrial food crop	Terrestrial	Food	Terrestrial	Occupational	Terrestrial	Terrestrial food & feed	Occupational
(2)	Terrestrial feed crop	terrestrial feed crop	Terrestrial	Food	Terrestrial	Occupational	Terrestrial	Terrestrial food & feed	Occupational
(3)	Terrestrial nonfood crop	terrestrial nonfood crop	Terrestrial	Nonfood	Terrestrial	Occupational	Terrestrial		Occupational
(4)	Aquatic food crop	aquatic food crop	Aquatic food	Food	Aquatic	Occupational	Aquatic	Aquatic food	Occupational
(5)	Aquatic nonfood residential	aquatic nonfood crop		Nonfood	Aquatic	Residential	Aquatic		Residential
(6)	Aquatic nonfood outdoor	aquatic nonfood outdoor	Aquatic nonfood outdoor	Nonfood	Aquatic	Occupational	Aquatic		Occupational
(7)	Aquatic nonfood industrial	aquatic nonfood industrial		Nonfood	Aquatic	Occupational	Aquatic		Occupational
(8)	Greenhouse food crop	greenhouse food crop	Greenhouse	Food		Occupational	Greenhouse	Greenhouse food	Occupational
(9)	Greenhouse nonfood crop	greenhouse nonfood crop	Greenhouse	Nonfood		Occupational	Greenhouse		Occupational
(10)	Forestry	Forestry	Forestry	Nonfood	Forestry	Occupational	Forestry		Occupational
(11)	Residential outdoor	residential outdoor	Residential outdoor	Nonfood	Outdoor residential	Residential	Residential outdoor	Residential outdoor	Residential
(12)	Residential indoor	indoor residential	indoor	Nonfood		Residential	Indoor		Residential
(13)	Indoor food	indoor food	Indoor	Food		Occupational	Indoor	Indoor food	Occupational
(14)	Indoor nonfood	indoor nonfood	Indoor	Nonfood		Occupational	Indoor		Occupational
(15)	Indoor medical	indoor medical	indoor	Nonfood		Occupational	Indoor		Occupational

Some comments on details:

- §158.100 lists a mysterious “(5) Aquatic nonfood residential” use pattern that doesn’t show up anywhere else. We can only speculate that this might be a tropical fish aquarium indoors or a koi fish pond in the yard, which wouldn’t seem to merit a separate category. Or perhaps it should be the “aquatic nonfood crop” category mentioned in Unit VIII.A of the Preamble (p. 12287a), which doesn’t otherwise have an exact match in §158.100. However, we are not aware of any intentionally planted nonfood crops, either.
- The “indoor medical” use pattern doesn’t occur in any of the subparts of the proposed rule. We presume this pertains to antimicrobial data requirements, which are to be revised subsequently.
- “Terrestrial food crop” and “terrestrial feed crop” uses are not separately distinguished in any of the charts. They should probably be combined in a single category.

- Ecotoxicology data requirements (§158.400) list specifically “aquatic food” and “aquatic nonfood outdoor” use patterns, leaving two other aquatic use patterns unaccounted for. The only real distinction of data requirements among the use categories are between indoor and outdoor uses.
- By comparison, the environmental fate data requirements (§158.1100) distinguish between “terrestrial” and “aquatic” uses, but not among the four separate aquatic categories.
- Toxicology data requirements (§158.500) list only two categories – “food” and “nonfood” – which generally don’t match the Subpart B list, but seem to be reasonably clear.
- Applicator and post-application exposure data requirements (Subparts K and U, §158.800 and §158.1500) distinguish only between occupational and residential uses, which is probably straightforward, but our interpretation above may miss some of the intended nuances.

Use Pattern Index (§159.1—(b), p.. 12332f)

The proposed rule moves the use pattern index, which associates each pesticide use pattern with the general use categories, from Appendix A of the current regulation to EPA’s web site, where it “will be updated periodically.” Since the association of a particular use pattern with a category ultimately determines the data requirements for approval of the product, the index must be included in the regulation where its content and updates are subject to notice-and-comment rulemaking under the Administrative Procedures Act. If the index is moved to a web site, data requirements for uses can be changed without proper oversight.

Required vs. Conditionally Required

The Preamble (Section VIII.B, p. 12287c) assigns to the “R” designation a probability greater than 50% that the study will be needed, while “CR” means a less than 50% probability. This is a surprising and disturbing revelation! According to the current regulation (§158.101):

“Data designated as “required” (“R”) indicates data for products with a given use pattern are needed by EPA to evaluate the risks or benefits for a product having that use pattern unless the data requirement has been waived under 158.45 for that particular product...”

The proposed revision retains much of the same language in 158.101, except that the statement about waivers is absent:

“Data designated as “required” (R) for products with a given use pattern are required by EPA to evaluate the risks or benefits of a product having that use pattern. Further clarification of the applicability of the data requirement often is located in the test notes accompanying the table.”

Waiver of “required” studies has always been an option under the regulations and CLA feels the same should be true under the revised regulation.

EPA must be very clear about which data are needed to reach a regulatory decision. Applicants have historically planned and budgeted for registration tasks years in advance of an intended application, basing decisions on the current §158.101, believing that studies designated as “R” are needed. They certainly do not wish to incur high costs and delays for studies that may be unnecessary up to 50% of the time, as this Preamble states. These Preamble statements along with the vagueness of many of the test notes for study requirements in the various subparts would make it necessary for each applicant to meet with Agency scientists to negotiate the actual data requirements for each new application on a case-by-case basis, up to years in advance of

actual submissions. Of course, it should always be possible for a registrant to have a pre-application conference with EPA to confirm what studies will definitely be required and which look reasonably subject to a waiver.

In addition, the statements in Preamble Section VIII.B significantly undermine the certainty of parties involved in data compensation negotiations; they imply that data that were generated, submitted, and evaluated by the Agency may not in fact actually need to be cited or relied upon by subsequent applicants, even though they are marked as “R” in the data requirement tables and were not waived. We suggest that, although the results of many studies may not be pivotal in reaching the final regulatory decision, such a decision cannot be adopted until the study has been conducted, reviewed, and considered by the Agency, so the Agency indeed does rely on them to eliminate the chance that a critical element of the assessment has been overlooked.

We request that EPA clearly restate the significance of the “R” and “CR” designations in the requirements tables in a manner that is consistent and interpretable by the applicant community. The “R” designation should be applied to studies that must be addressed by submission of either data or a scientifically reasoned waiver request. Each of the study requirements and corresponding test notes should be reevaluated in light of this interpretation.

Identifying Data for Experimental Use Permits (EUPs)

The use of brackets uniformly in all data requirements tables as has been done in the past is an adequate way to distinguish EUP data needs from Section 3 data needs, though we would encourage the Agency to continue searching for improvements. For consistency, brackets should be added to the requirements in Subpart D (product chemistry) to indicate that all requirements are necessary for EUP submissions. Subpart O (residue chemistry) presents some special challenges in this regard, as explained in more detail in our comments on that topic. Subparts K (post-application exposure) and U (applicator exposure) are silent on the subject of requirements for EUPs. If indeed none of those studies are required for EUPs, a note in the respective subparts to that effect would be helpful.

Use of Test Notes in Tables

Subpart D gives explanatory details about conditions for requiring individual studies in a mixture of test notes and subsequent text sections, while other subparts give those explanatory details primarily in test notes. Many of the test notes for the product chemistry data requirements table in Subpart D simply refer the reader on to subsequent sections in the text of the regulation. The Agency should consider making the format of all of the subparts consistent. It might be a better approach overall to replace all test notes with the subsequent paragraphs, which would be noted in the data requirements tables. For example, for “product chemistry and composition,” the last column of the table would refer the reader directly to §158.320, rather than first to test note 1 and then to §158.320.

Subpart D—Product Chemistry

Product Chemistry (§158.310)

While §158.310(a)(3) indicates that all of the product chemistry data are required to support an EUP, brackets should be used consistently in all tables to denote EUP requirements explicitly.

Preliminary Analysis (Guideline 830.1700)

The Agency's position on the necessity of these analytical data is poorly explained in the proposed rule (§158.345, p. 12339d). The following details need to be clearly spelled out in the regulation: (1) If the product is a technical grade of the active ingredient (TGAI), analytical data on five batches are needed; (2) if the product is a (manufacturing-use product (MP) or end-use product (EP), and it is prepared from a registered active ingredient (AI) source product, analytical data to confirm the AI level are not required; and (3) if the product is an EP or MP made via an integrated system, and the TGAI cannot be separately isolated for analysis, then preliminary analysis data are required to confirm the AI level in the EP.

Practically speaking, because the regulation requires a validated enforcement method, storage stability data, and determination of test material stability for GLP compliance, registrants must conduct product analyses for AI content. Good product stewardship also requires this capability. In light of the immense scope of the pesticide registration data requirements, perhaps the Agency should reconsider and institute a simple requirement for preliminary analysis data.

UV/Visible (Guideline 830.7050)

Test notes for this study and the “photodegradation in water study” (Guideline 835.2240, §158.1100(d), p. 12349a) should link the two studies with the information from Unit IX.B.2.i of the Preamble (p. 12288b).

Particle size analysis (Guideline 830.7520)

Test note 24 indicates these data are needed for all insoluble substances and for fibers with particle diameter $\geq 0.1\mu\text{m}$, purportedly relating to drift concerns (see Preamble Unit.IX.B.2.ii; p. 12288c). It is unclear why this data would be useful for any sprayed application, since the total non-volatile proportion needed to estimate off-target deposition in the AgDRIFT model is the field exposure droplet or dried final particulate, not the particle size of the TGAI or PAI. No TGAI or PAI data would fit EPA's stated purpose, since the particle size distribution relevant for off-target spray drift is the distribution of spray droplets produced by the application equipment. For dusts or granules, the particle size distribution of the formulated product (but not the TGAI or PAI) may be relevant to the environmental risk assessment. An upper limit on fiber diameter of, say, 95% $> 200\text{-}\mu\text{m}$ diameter would minimize the off-target exposure potential. EPA has not made it clear what data on fiber size are requested to meet an unstated risk assessment need. EPA should be aware that the particle size distribution of some products may be considered proprietary business information. We agree that the data requirement should be conditional and usually should be applied only when formulated products are applied as solids and have the potential for producing dust.

Partition coefficient (Guidelines 830.7550, et al.)

The Preamble (Unit IX.3.iii, p. 12288d) indicates that partition data are not needed if the substance hydrolyzes or is completely soluble. However, test note 25 indicates the data aren't needed if the compound dissociates or is partially or completely soluble. These conditions seem both vague and inconsistent. Hydrolysis and dissociation are not the same phenomenon. We recommend that the partition data be "Required for organic substances with maximum water solubility below 10 g/L (unbuffered) but not required for substances that breakdown hydrolytically (> 50% in 24 hours) under conditions of the test."

Product Chemistry Data Requirements for Groups of End-Use Products

An option for reducing product-specific chemistry data should be provided for logical groups of end-use products containing the same active ingredient(s) and inert ingredients system, varying only in the concentration of active ingredient(s). Consider a series of aqueous-based products containing 1%, 5%, 10%, and 20% of the same active ingredient, differing only in the amount of water and active ingredient. The full array of applicable data would be provided for representative products of the group and reduced data would be provided for other products in the group. For example, ranges of concentrations could be bracketed by product chemistry testing of the highest and lowest concentration products. Selected product chemistry studies would then be conducted as needed on the various individual products in the group, such as density, pH, and flash point (if the product is or contains a flammable or combustible liquid). A new paragraph under §158.310 could explain that reduced testing of a related group of products is permissible under such circumstances with submission of an appropriate grouping rationale.

General Comment (guidance that may be missing)

One missing item is guidance on the preparation of Confidential Statement of Formula (CSF). §§158.320 and 158.325 generally discuss the elements of the CSF, but they do not define at all how to translate this information into Form 8570-4. The purpose of the CSF form in relation to the actual Series 830 data elements is not explained, nor is the process for amending the registration by changing inert ingredient compositions through amending a CSF.

Since the CSF provides the means for submitters to comply with the Guideline 830 series data elements, providing clear guidance regarding this process in Subpart D would alleviate a significant potential source of confusion both among registrants and regulatory staff.

Subpart E - Terrestrial and Aquatic Nontarget Organisms

General Comments

Currently the official guidance documents for ecological testing are the Ecological Effects Branch (EEB) 71 series for avian and wild mammal toxicity studies. CLA has submitted detailed comments to EPA and documented the lack of harmonization between the draft, OPPTS guidance (850 series) and the expectations of USEPA Environmental Fate and Effects Division (EFED) for the terrestrial and aquatic nontarget organism data packages. This disagreement between the OPPTS guidance and current OPP expectations is confirmed based on EFED risk assessments for new compounds, the Data Evaluation Records (DERs) for new compound submissions, and the latest Reregistration Eligibility Documents (REDs). Had industry followed the 850 guidance for these terrestrial toxicity studies the EFED reviewers would not be satisfied with the data submissions. CLA proposes that both guidance documents (850 series and 71 series) be noted in the data requirement tables until such time that the 850 series guidance is revised to reflect the EFED reviewers' requirements for these toxicity studies. This proposed change is reflected in CLA Tables 1 and 2.

As with all new requirements, studies should not be requested until finalized guidelines and/or protocols are available. This is of particular concern in the passerine testing requirement (Avian oral toxicity) and the chronic sediment study requirement.

CLA also reiterates the need for harmonization with the international community.

In the data requirements for terrestrial or aquatic field studies, EPA has proposed a requirement for interlaboratory validation of analytical methods. An ILV for analytical methods likely to be of use by federal and state agencies engaged in chemical monitoring programs is submitted to EPA as part of the overall data package on the active ingredient. Field studies are not routinely conducted by government agencies or even registrants; therefore, it does not make sense to conduct a separate ILV of the analytical methods used in such studies. This represents an inappropriate and expensive change to the data requirement with little foreseeable societal benefit.

Avian and Mammalian Testing

In order to clarify the requirements for avian toxicity tests with TGAI and TEP, each row for the guideline numbers should be split into two rows. CLA Table 1 outlines the CLA proposed changes to the terrestrial portion of the Terrestrial and Aquatic Nontarget Organism Data requirements table. In general, tests with the TGAI are required for outdoor uses, and conditionally required for greenhouse or indoor uses. Tests with the TEP should only be conditionally required for outdoor uses. Test notes and appropriate table references were modified to reflect the CLA proposed changes.

A proposed new study requirement is the avian acute oral LD50 in a passerine species, the preferred species being the redwing blackbird (*Agelaius phoeniceus*). For the vast majority of chemicals developed for use as pesticides, testing with bobwhite or mallard provides adequate data for use in risk assessment. The agency currently has methodology for extrapolating the results of tests with bobwhite quail to small passerine species such as the red-winged blackbird.

Performing actual tests with such species should be reserved for the few cases where it is crucial to reduce uncertainty inherent in existing extrapolation methods. When a test with a passerine species is needed, the preference for a redwing blackbird to the exclusion of all other passerines is unnecessarily restrictive. The Agency should allow flexibility in the selection of passerine species to accommodate the difficulty of contract laboratories to maintain populations of or obtain locally the test species and also to allow registrants to test species relevant to the locality of the end use. Because avian species vary widely over the geographic regions of the United States, avian testing requirements should remain flexible. The Agency is encouraged to publish a list of acceptable species instead of selecting a single species. Registrants should use this list to identify and justify a relevant passerine species on a case-by-case basis.

CLA proposes the following modification to the “Simulated or Actual Field Testing” row. The test note, number 9, should be revised or eliminated from the requirements for this study. Analytical measurements may be included in ecotoxicology field studies. However, an independent laboratory validation (ILV) of this specific analytical method is a new requirement for studies covered by §158.400. As stated in the general comments above, an ILV for analytical methods likely to be of use by federal and state agencies engaged in chemical monitoring programs is submitted to EPA as part of the overall data package on the active ingredient. Terrestrial field studies are not routinely conducted by government agencies or even registrants; therefore, it does not make sense to conduct a separate ILV of the analytical methods used in such studies. This represents an inappropriate and expensive change to the data requirement with little foreseeable societal benefit.

CLA Table 1. CLA proposed changes to Terrestrial Nontarget Organism Data Requirements

Guideline Number	Data Req.	Terrestrial	Aquatic Food	Aquatic Nonfood Outdoor	Aquatic Nonfood Residential	Forestry	Residential Outdoor	Green-house	Indoor	Test Substance	Test Note
850.2100; 71-1	Avian Oral	[R]	[R]	[R]	R	[R]	[R]	CR	CR	TGAI	1,2,4
	Avian Oral	CR	CR	CR	CR	CR	CR	NR	NR	TEP	3
850.2200; 71-2	Avian Dietary	[R]	[R]	[R]	CR	[R]	[R]	NR	NR	TGAI	1,5,6
	Avian Dietary	CR	CR	CR	NR	CR	CR	NR	NR	TEP	3
850.2400; 71-3	Wild mammal	CR	CR	CR	NR	CR	CR	NR	NR	TGAI	7
850.2300; 71-4	Avian Repro.	R	R	R	NR	R	R	NR	NR	TGAI	1,5
850.2500; 71-5	Simulated or Actual Field test	CR	CR	CR	NR	CR	CR	NR	NR	TEP	8, 9

Insect Pollinator Testing

The Agency proposes to conditionally require field testing for pollinators for terrestrial (feed crop) and aquatic nonfood (aquatic outdoor and residential) uses where honeybees are likely to be exposed to pesticides. It should be noted that DRAFT guideline 850.3040 is extremely vague. Test note 26 of the data requirements table lists conditions proposed to trigger this study. These conditions are quite broad, suggesting that a full field test could be requested frequently. In particular condition iii: “Data derived from studies with arthropods other than bees that indicate potential chronic, reproductive, or behavioral effects” is unnecessarily broad. CLA submits,

whereas studies on other *Hymenoptera* (or perhaps other social insects) might raise legitimate concerns over bee toxicity, this note suggests that a bee field study could be requested even if a chronic effect was seen only in an aquatic invertebrate. A narrowing of this definition is needed. Further, CLA suggests a tiered approach to evaluating potential effects of pesticide exposure to pollinators, with the initial testing being conducted under semi-field conditions (e.g.; a tent or tunnel) rather than progressing immediately to a full-scale field test.

Aquatic Organism Testing

The Preamble Unit X.3.vii, Chronic toxicity (p. 12290e), proposes to separate the freshwater and saltwater requirements, but does not include a description of the saltwater testing.

Currently Part 158 requires two freshwater fish studies with the TGAI to support terrestrial and aquatic (food crop and nonfood), forestry, and domestic outdoor uses and conditionally requires one of these studies for greenhouse (food crop and nonfood) and indoor uses. The new rule seems to suggest that a second fish species would be required to support greenhouse and indoor uses. This is clearly supported in Table 3, however EPA should review the text description for clarity.

In order to clarify the requirements for aquatic toxicity tests with TGAI and TEP for freshwater and marine/estuarine organisms, each row for the data requirements should be split into two rows to separate the test substance. CLA Table 2 outlines the CLA proposed changes to the aquatic portion of the Terrestrial and Aquatic Nontarget Organism Data requirements table. The rationale for the conditional requirement for TEP testing is explained in the proposed changes to the test notes (see test note 11). Test notes and appropriate table references were modified to reflect the CLA-proposed changes.

Sediment Testing Requirement

It is stated in the rule that "...effects of sediment bound pesticides ... on aquatic environments cannot be accurately assessed from bioassays on compounds suspended in the water column alone..." We respectfully request that the agency justify this statement. A well accepted theory (Equilibrium Partitioning, EqP), published by EPA (DiToro, et. al. 1991, Environ. Toxicol. Chem. 10:1541-1583), exists that links water column concentrations to sediment concentrations, allowing one to assess the impact of bound pesticides. The agency needs to recognize that sediments are complex environments, and that it is often difficult to characterize exposure in terms of the bioavailable fraction; uncertainty is not necessarily reduced by performing sediment toxicity studies. Prior to requiring sediment toxicity studies, the agency should perform sediment risk assessment utilizing water column toxicity data and an understanding of the pesticide's behavior in the environment. Only when such an assessment leads to substantial uncertainty should sediment toxicity testing be initiated.

It is difficult to assess EPA's triggers for sediment toxicity testing due to inconsistencies in the document. The triggers are reported in Unit X.B.2.i and ii (p. 12289d) and §158.400(e), test notes 23 and 24 (p. 12345c). The trigger for "acute" testing is reported to be a $K_d \geq 50$ mg/L and a half life of ≤ 10 days. There appears to be a typographical error and should have read ≥ 10 days. For "chronic" testing the trigger is a half-life " \geq " 10 days, along with $K_d \geq 50$ mg/L, and a reference to the acute sediment studies ($EEC \geq$ "acute" sediment EC_{50}/LC_{50}), implying that a

acute study must be done prior to conducting the chronic. Clarification of the triggers is necessary in order to evaluate the proposed testing requirement. Three factors, adsorption, persistence, and toxicity, are important in determining whether a compound is of potential concern in the sediment. All three factors should be considered when setting triggers for sediment toxicity testing. The Agency should clearly specify the conditions for both acute and chronic testing.

In the proposed rule, EPA states that the sediment testing requirement would not be commonly required. However, the EPA proposed trigger levels are quite liberal and a large number of compounds, including those where no sediment concern has been identified, would trigger testing. The trigger $K_d \geq 50$ mg/L is quite low, and inconsistent with current scientific knowledge. A value of $\log K_{ow} > 3$ is more commonly used to judge whether a compound might have adsorptive potential. It is also strongly recommended that, in the interest of harmonization, the Agency consider adopting the triggers used in the EU to initiate sediment toxicity testing for pesticides.

It should also be noted that the Agency's proposed requirement for spiked sediment is counter to what is currently being performed in the EU, and results in less harmonization and additional studies to address the same basic risk question. Currently in the EU, sediment toxicity studies with a spiked water design are widely utilized. It is proposed that the Agency, instead of imposing a new study design, utilize an existing study design that is being widely used by the regulatory community.

It would be helpful if the Agency clarified its definitions of "acute" and "chronic" sediment toxicity studies. The "acute" sediment testing guidelines most commonly used in the USA are more analogous to a "chronic" Fish ELS (mortality and growth are measured), than to acute fish or daphnia studies. The typical duration (> 10 days) of most sediment toxicity studies represents a significant portion of the typical test organism life span, again suggesting that the studies should be considered more representative of chronic effects, rather than acute. Nomenclature is important to determine the appropriate incorporation in the risk assessment.

Accumulation Studies in Aquatic Nontarget Organisms

The triggers for a accumulation study in aquatic nontarget organisms are not clear and include "Required if significant concentrations of the active ingredient and/or its principal degradation products are likely to occur in aquatic environments and may accumulate in aquatic organisms." The agency needs to clarify the two data requirements in Subpart E and Subpart N in terms of potential accumulation testing with aquatic organisms. Neither footnote in either Subpart adequately expresses the triggers for conducting this test. The triggers for this test need to include the potential for exposure as well as the potential for accumulation, which are clarified in the test notes for the fish bioaccumulation test. Additionally, a list of potential organisms for the test should be included.

CLA Table 2.. CLA proposed changes to Aquatic Nontarget Organism Data Requirements											
Guideline Number	Data Req.	Terrestrial	Aquatic Food	Aquatic nonfood Outdoor	Aquatic Nonfood Residential	Forestry	Residential Outdoor	Greenhouse	Indoor	Test Substance	Test Note
850.1075 72-1	Freshwater fish toxicity	[R]	[R]	[R]	R	[R]	R	CR	CR	TGAI	1, 2, 10
850.1075 72-1	Freshwater fish toxicity	CR	CR	CR	CR	CR	CR	CR	CR	TEP	11
850.1010 72-2	Acute toxicity freshwater invertebrates	[R]	[R]	[R]	R	[R]	R	CR	CR	TGAI	1, 2, 12
850.1010 72-2	Acute toxicity freshwater invertebrates	CR	CR	CR	CR	CR	CR	CR	CR	TEP	1, 2, 12
850.1025 850.1035 850.1045 850.1055 850.1075 72-3	Acute toxicity estuarine and marine organisms	R	R	R	NR	R	R	NR	NR	TGAI	1, 13, 14
850.1025 850.1035 850.1045 850.1055 850.1075 72-3	Acute toxicity estuarine and marine organisms	CR	CR	CR	NR	CR	CR	NR	NR	TEP	11, 13, 14
850.1300 72-4	Aquatic invertebrate life-cycle (freshwater)	R	[R]	[R]	NR	[R]	CR	NR	NR	TGAI	1, 12, 14
850.1350 72-4	Aquatic invertebrate life-cycle (saltwater)	CR	CR	CR	NR	CR	CR	NR	NR	TGAI	14, 16, 17
850.1400 72-4	Fish early-life stage (freshwater)	R	[R]	[R]	NR	[R]	CR	NR	NR	TGAI	1, 14, 15
850.1400 72-4	Fish early-life stage (saltwater)	CR	CR	CR	NR	CR	CR	NR	NR	TGAI	14, 17, 18
850.1500 72-5	Fish life-cycle	CR	CR	CR	NR	CR	CR	NR	NR	TGAI	19, 20
850.1710 850.1730 850.1850 72-6	Aquatic organisms bio-availability, bio-magnification, toxicity	CR	CR	CR	NR	CR	NR	NR	NR	TGAI, PAI, degradate	21
850.1950 72-7	Simulated or actual field testing for aquatic organisms	CR	CR	CR	NR	CR	CR	NR	NR	TEP	9, 22
Sediment Testing											
850.1735	Whole sediment: acute freshwater invertebrates	CR	CR	CR	NR	CR	NR	NR	NR	TGAI	23
850.1740	Whole sediment: acute marine invertebrates	CR	CR	CR	NR	CR	NR	NR	NR	TGAI	23
--	Whole sediment: chronic invertebrates fresh-water	CR	CR	CR	NR	CR	NR	NR	NR	TGAI	24
--	Whole sediment: chronic invertebrates marine	CR	CR	CR	NR	CR	NR	NR	NR	TGAI	24

Test Notes

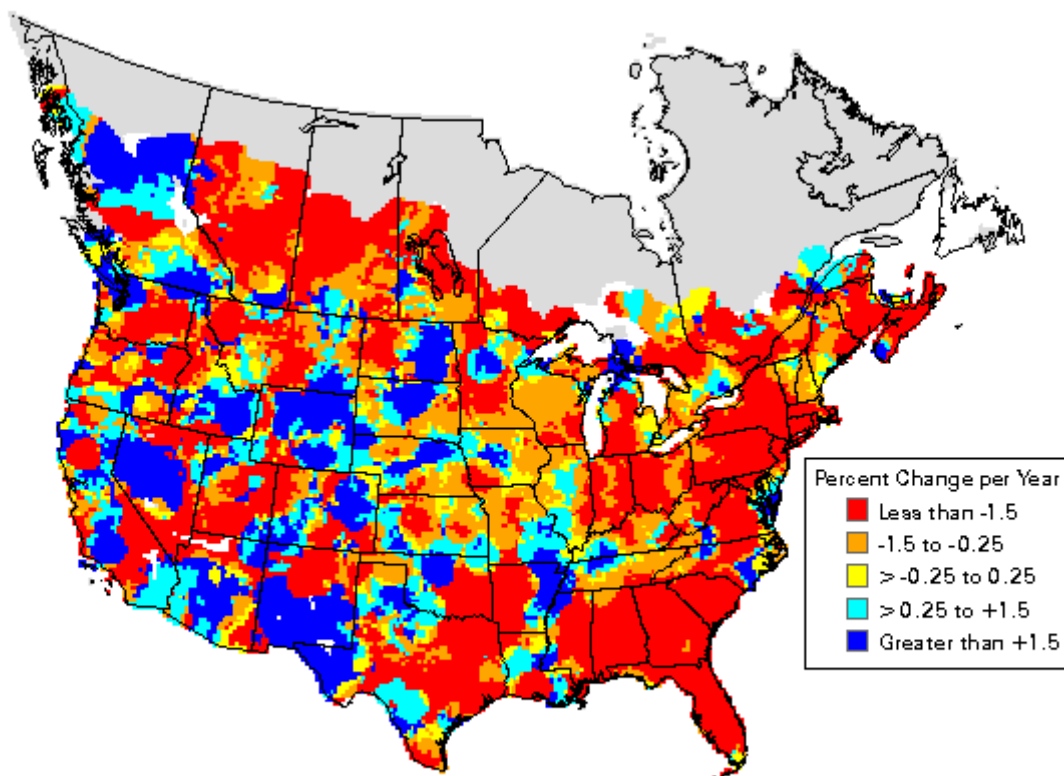
Test Note 3: The TEP testing for avian species should only be triggered when the nontarget terrestrial organism is expected to encounter the intact end-use formulation in the environment or is expected to use the formulation itself as a food source, and the risk of adverse effects in such a situation is potentially high ($RQ > 0.5$) based on calculations using the toxicity of the TGAI. Possible examples of an end-use formulation that may trigger TEP testing are seeds, granules and pellets.

CLA proposes the following change to test note 3: Data using the TEP are conditionally required based on the results of the avian acute oral (TGAI) and avian subacute dietary tests (TGAI), the potential for oral ingestion of the end use formulation, and an acute $RQ > 0.5$.

Test Note 4: The Agency is proposing a significant expansion of the avian testing requirements by requiring acute oral toxicity tests with 2 species, the red-winged blackbird and either the mallard or bobwhite quail for all pesticides with outdoor uses. Currently only 1 test, usually performed on the bobwhite or mallard, is required. The additional requirement of a test with red-winged blackbirds is ill-advised because this is a wild species that is not easily obtained in the numbers that will be required for routine testing, nor is it a species easily maintained under laboratory conditions. Although it is a common North American species, its populations are declining throughout much of North America according to the USGS Breeding Bird Survey results (the areas in red and orange in the population trend figure below). Wild animals should only be used for toxicology tests when absolutely necessary. For the vast majority of chemicals developed for use as pesticides, testing with bobwhite or mallard provide adequate data for use in risk assessment. The agency currently has methodology for extrapolating the results of tests with bobwhite quail to small passerine species such as the red-winged blackbird. Performing actual tests with such species should be reserved for the few cases where it is crucial to reduce uncertainty inherent in existing extrapolation methods.

BBS reference: <http://www.mbr.pwrc.usgs.gov/bbs/htm03/trn2003/tr04980.htm>

Red-winged Blackbird *Agelaius phoeniceus* BBS Trend Map, 1966 – 2003



CLA proposes the following change to test note 4: Data are preferred on mallard or bobwhite quail for all uses. Additional species may be tested on a case by case basis to reduce uncertainty about the toxicity of the chemical to wild species.

Test Note 6: The dietary TGAI testing for aquatic non-food residential uses should only be triggered when the nontarget terrestrial organism is expected to be exposed in the environment and the terrestrial acute risk assessment results trigger a potential concern based on the acute oral test with the TGAI.

CLA proposes the following changes to test note 6: For aquatic nonfood residential uses, if the TGAI acute avian risk assessment indicates a significant concern for a given use and there is a potential for exposure, then an additional acute dietary test with TGAI may be conducted using either bobwhite quail or mallards.

Test Note 7: Wild mammal studies should only be triggered when the terrestrial risk assessment triggers a potential concern based on the mammalian endpoints generated in the toxicology data package. The number of mammals sacrificed in the toxicology data package is quite extensive. The language of this footnote should be more specific in order to only require additional testing with wild mammal species when the risk assessments trigger a concern.

This is in keeping with the Agency's commitment to Animal Welfare Concerns and reducing animal testing, when possible.

CLA proposes the following changes to test note 7: Data on wild mammal species may be required when a refined terrestrial risk assessment results trigger a potential concern for a given use pattern based on laboratory toxicity endpoints and a refined exposure assessment. Consideration needs to be given to the potential for exposure and the potential assessment endpoints that could be impacted.

Test Note 8: Additional testing, particularly with wild species in the natural environment, should only be conducted when refined terrestrial risk assessments indicate a potential concern. Using a risk based trigger ensures that these studies are only performed when all other ecotoxicological tools and processes have indicated that field data is required to resolve uncertainties in the terrestrial risk assessment.

CLA proposes the following changes to test note 8: Higher tier testing may be required for a specific use pattern when a refined terrestrial risk assessment indicates a concern based on laboratory toxicity endpoints and refined exposure assessments.

Test Note 9: Industry conducts independent laboratory validation (ILV) as an EPA requirement when registering crop protection chemicals. The methods developed to support guideline studies on target and rotational crops, soil, water, and animal tissues are verified for use in chemical monitoring programs across the US. Typically, the ILV studies (usually only one or two are conducted) support all method development for all matrices in the submission package. It is very unlikely that any method required for an ecotoxicological field study sample would meet the EPA triggers for a separate ILV study. The CLA proposed language clarifies that field study samples are not expected to significantly vary in methodology from those covered by the ILV work required by other scientific disciplines in HED and EFED.

CLA proposes the following changes to test note 9: Analytical chemistry methods to support higher tier Ecotoxicology studies, must be based on the environmental chemistry methods (with ILV) that are available to EPA as part of the submission package for the active ingredient.

Test Note 11: The Agency proposes in test note 11 the potential triggers for EP or TEP testing for freshwater and marine organisms. Potential aquatic exposure to an EP or TEP would result from either a direct application scenario or highly significant spray drift event. The aquatic organism would not be exposed to the intact EP or TEP from a runoff scenario. Current models do not have the capability to express the exposure of the EP or TEP components other than the TGAI. Therefore these tests are not relevant for risk assessments from runoff exposure. In order to conserve organisms, a tiered approach to the testing with EP and TEP is proposed. The first tier of test would be for the TGAI with freshwater and marine organisms. Assuming appropriate triggers are reached and no difference in sensitivity between the freshwater and marine organisms, the second tier of tests would include EP or TEP with the freshwater organisms. The third tier of tests would be for the marine/estuarine organisms if the marine/estuarine organisms demonstrated greater

sensitivity in the first tier. Additionally, the exposure estimates for the decision for marine testing should be based on potential exposure in marine/estuarine environments. While the models for the marine exposure estimates are not finalized, the Part 158 should indicate that this should be the basis for the decision.

CLA proposes the following triggers for EP and TEP testing for freshwater organisms:

- i. direct application of the EP to the freshwater environment, OR
- ii. significant spray drift resulting in the maximum estimated environmental exposure in the freshwater environment to be greater than one-half of the LC50 or EC50 of the TGAI testing with freshwater organisms, OR
- iii. an ingredient in the EP or TEP is expected to enhance the toxicity of the active ingredient.

CLA proposes the following the following triggers for marine testing with EP or TEP:

- i. direct application of the EP to the marine/estuarine environment, OR
- ii. significant spray drift resulting in estimated environmental exposure in the marine/estuarine environment to be greater than one-half of the LC50 or EC50 of the TGAI testing with marine/estuarine organisms,

AND

- iii. the EP or TEP testing that was triggered for freshwater organisms indicate that the EP or TEP may have greater toxicity than the TGAI, OR
- iv. the marine/estuarine tests with the TGAI indicate that marine/estuarine organisms are more sensitive than the freshwater organisms, OR
- v. an ingredient in the EP or TEP is expected to enhance the toxicity of the active ingredient.

Test Note 13: *Menidia* sp. is listed as the preferred species for the saltwater acute study whereas the sheepshead minnow is listed as preferred for the early life-stage study. This seems inconsistent with EPA's desire to progress from acute to subchronic (and chronic) testing with the same species as EPA refers to in test note 15. *Menidia* sp is also a more labor-intensive laboratory species.

CLA recommends changing the preferred species for acute saltwater testing to the sheepshead minnow (*Cyprinodon variegatus*).

Test Note 15: The Agency states that the rainbow trout is the preferred species for the freshwater ELS study. If the fathead minnow is used, a 96-hr LC₅₀ on fathead minnow must also be submitted. While the fathead is an acceptable warm water species under OPPTS 850.1075, bluegill is the preferred warm water species for the acute test. Many ELS studies are performed with fathead minnow, which means that fathead minnow acute studies will increasingly be substituted for the bluegill acute study. While this apparently will meet EPA's guidance, EPA should be aware of this possible increased substitution. Logically, it seems that EPA should revisit the preferred species for the ELS and reconsider fathead minnow and also reconsider the preferred species for the acute warmwater fish test and reconsider fathead minnow over bluegill. This change would seem to provide the

consistency the agency is seeking between test species at the acute, subchronic and chronic testing methods.

Test Note 16: The nomenclature ‘*America mysis*’ appears to be misspelled and is likely meant to read ‘*Americamysis bahia*’. It should be noted that the USDA Integrated Taxonomic Information System (ITIS; <http://www.itis.usda.gov>) does not list any species with the name ‘*America mysis*’ or ‘*Americamysis*’ and only lists *Mysidopsis bahia* (Taxonomic Serial No. 90140) as the valid name. To avoid confusion, the name *Mysidopsis bahia* which is recognized by the USDA ITIS database, should be considered an equally valid alternative and not simply as a former name.

Test Note 19: The potential triggers fish life cycle testing for marine/estuarine species should be consistent with test note 20. CLA recommends a consideration of the sensitivity differences between freshwater and marine/estuarine species to determine the most appropriate test organism. The preferred species for either freshwater or marine/estuarine testing are not listed in the test note. It is suggested the preferred freshwater species be the fathead minnow (*Pimephales promelas*) and the preferred marine/estuarine species be the sheepshead minnow (*Cyprinodon variegatus*).

Data Requirements Specific to Endangered Species Assessments and Determinations (Unit X.C, pp. 12291-12292]

CLA fully supports EPA’s plans to require data specifically for endangered species assessments and determinations. However, CLA believes that considerably more transparency is needed in Part 158 to characterize exactly what data are necessary and under what circumstances they should be required. In Pesticide Registration Notice 2000-2, the formation of an industry task force (FIFRA Endangered Species Task Force, FESTF) is announced. The FESTF was formed in response to EPA data requirements related to the potential impact of pesticides on listed species. The PR Notice communicates the various options associated with meeting the EPA data requirements that are currently pending for some pesticides as well as any future cases that may be imposed on registrants through the registration or reregistration process. This communication provided the general framework (the work products of the task force or the equivalent completed by an individual registrant), however the PR Notice does not provide ample detailed guidance on what exact information will be required of the registrant in order to satisfy a Data Call-In for endangered species data for a specific pesticide. The Agency notes, in the proposed rule, that the industry task force database may partly fulfill Agency needs. In other words, existence of this generic information management tool and underlying databases alone may not completely fulfill an endangered species data requirement triggered by a regulatory action for an active ingredient. The revision of Part 158 provides the opportunity to explicitly establish the conditions for the Agency requiring the data and to describe in a guidance document exactly what data is required from a registrant, in order to fully satisfy the data requirement. Certainly, the work products of FESTF will be integral to the registrant in satisfying their data requirements and to the Agency in reviewing the data submission and completing the endangered species effects determination. However, registrants need transparency as to exactly what information will satisfy a pesticide

specific Data Call-In and how this data will be used by the Agency in the endangered species assessment process.

Furthermore, CLA recommends that registrants and other affected stakeholders understand exactly what type of information is being required, when it is required, and also the standards of quality that the data must meet, in order to support EPA's development of effects determinations for endangered species. A transparent approach with clear conditions for requiring the data requirement, supported by guidance documents would be consistent with the transparency associated with Conditionally Required (CR) data within Part 158. In other words, endangered species should not be treated differently as "special studies" requested on a case-by-case basis, that lack the transparent quality procedures that govern Conditionally Required data in Part 158. "Special Studies" typically have no transparent conditions for when they are necessary and often take considerable time and resources (on the part of the registrant and EPA) to develop acceptable protocols on a case-by-case basis. This type of approach appears inconsistent with EPA's intent to fulfill its obligations to expediently conduct high quality effects determinations for endangered species using best available data under the new Joint Counterpart ESA Regulations. Clearly articulated data requirements, with established conditions for when these are required, codified in Part 158 to provide transparency to all affected stakeholders, and supported by guidelines would increase the quality and efficiency of EPA's endangered species assessment process.

The Agency should codify requirements for endangered species in Part 158 as Conditionally Required studies. Conditions for requiring endangered species data should be based on the proposed uses of the pesticide. Endangered species data should not be required for indoor, greenhouse or other uses where there is high certainty that these uses would not result in exposure to listed species. Endangered species data should be required for other uses of pesticides where there is potential for exposure to endangered species and where EPA must conduct a refined species-specific assessment because screening-level ecological risk assessments show exceedances of levels of concern for endangered species.

As previously stated above, the Agency should develop a guidance document that describes how the registrant is to provide information on proximity of pesticide use to locations of endangered species to meet quality standards irrespective of whether the registrant chooses to use the industry task force system or some other means. The industry task force's system can be used by the registrant in satisfying its data requirements for a specific pesticide in an effective and efficient manner. This system evaluates the spatial relationships of use site and species location, and the circumstances that exist to exclude the need for species evaluation (species biology, site-specific general conditions, etc.). Clearly, the Agency needs to provide guidance (including quality criteria) on use of this tool and the submission of information by the registrant to fully satisfy endangered species data requirements imposed on their active ingredient. The EPA Overview Document (supporting the Joint Counterpart ESA Regulation) provides a general description of tools and risk assessment, but does not specifically define a standard procedure for applying these tools (a hierarchy of what to examine first, and what triggers the need to go to a higher level of evaluation). Developing a standard operating procedure or guideline would bring uniformity to the assessment and transparency to the outcome.

The Agency communicates in the proposed rule that they and the Services have identified additional research areas that may be necessary to effectively characterize potential risks to listed species from pesticide use. Any new data requirement resulting from future research endeavors should certainly be considered in the context of its utility within the endangered species risk assessment process. Whether used in a qualitative or quantitative manner, any additional studies using research animals as well as incurring significant cost to the regulated community should provide an incremental benefit to the protection of listed species and not negatively impact the users of pesticides. The conduct of any future research to address these apparent uncertainties needs to be a transparent process. Should any of these research areas result in the development of new data requirements, a transparent process must also be utilized to insure that clear triggers in the data generation process are identified and standard protocols are developed following completion of the research. The Information Management Tool (IMS) described above provides a uniform approach to access the required data for individual active ingredients. Additional higher tiered data, including individual species surrogate testing with standardized protocols, should be at the option of the registrant based on the level of mitigation a given registrant is willing to accept (or defend) for its own product.

Research should be conducted through appropriate mechanisms and not as a condition of registration. However where methods are available, additional data requirements (e.g., toxicity data, pesticide use information) could be generated by the registrant if it is necessary to refine/reduce uncertainty in the endangered species assessment for an active ingredient. Otherwise there should be no requirement. As an example, if the proximity information shows no co-occurrence of a pesticide use and a listed species then there is no added value to generating costly data and there should be no data call-in for that pesticide registrant to generate such data.

EPA should use the Agency established risk assessment process to identify research priorities in order to ensure that any additional information generated will have a significant impact on refining the species-specific assessment. These research areas should be relevant to measures for assessment endpoints in the problem formulation for the endangered species assessment and also relevant conceptual models and routes of potential exposure that should be explicit in the problem formulation. Specifically,

- A costly survey to generate product use information that is time-limited at a county-level is unlikely to be worthwhile. Existing pesticide use information on a larger geographic scale such as a Crop Reporting District (CRD) may well add value to the assessment.
- The process should consider the end use product formulation. Clearly there is no value in generating additional data on end use products if the formulation has no properties that increase toxicity or exposure compared to the active ingredient. Data requirements for end use products have been addressed earlier in the CLA comments for terrestrial and aquatic organisms.
- Generation of toxicity data on a more relevant surrogate for listed species potentially affected by use of the pesticide may be of considerable value if applicable to a large number of locations of the listed species that overlap with potential uses of the pesticide. However, rather than focusing on critical life stages, perhaps there should be instead a concern based on toxicological sensitivity. Current acute and long-term studies address toxicologically-sensitive life stages in birds and mammals, crustaceans, fish, aquatic non-vascular plants, and terrestrial vascular plants.

- Generation of detailed dose-responses, measurements of physiological, biochemical, and morphological characteristics of endangered species to refine interspecies extrapolations have questionable value in a species-specific refinement as it is unlikely to reduce uncertainty that has been addressed by safety factors in screening-level risk assessments. Similarly, data to determine interspecies sensitivity for non-target plants have questionable value; however, data to better estimate exposure for non-target plants may have greater potential value.

Additional data to refine the species-specific assessment should be defined on a case-by-case basis and relevant to the refined problem formulation for the compound under evaluation. Only data that are most likely to have greatest impact in refining the assessment should be developed. There should be no requirement for data that have minimal or no impact on the overall species-specific refinement.

Subpart F – Toxicology

ILSI/HESI “Agricultural Chemical Safety Assessment” Recommendations [Unit XXI]

CLA commends the Agency’s significant participation in and contributions to the ILSI Health and Environmental Sciences Institute (HESI) project, “Developing Strategies for Agricultural Safety Evaluation.” As noted in Unit XXI of the Preamble (“ILSI Work on New Toxicity Paradigm”), the HESI project brought together international scientific experts from government, academia, and industry to propose improvements in the efficiency and accuracy of the current testing paradigms for agricultural chemicals. The HESI work group has proposed a tiered approach that incorporates existing knowledge on the chemistry, toxicology, and actual human exposure scenarios and integrates studies on metabolism/kinetics, life stages, and systemic toxicity. The tiered approach may significantly reduce the number of animals required in tests to provide a thorough health assessment of these products. Draft versions of the HESI proposals currently are available on the HESI web site and final versions will be published soon in the journal *Critical Reviews in Toxicology*.

Although the Preamble acknowledges the HESI project, there is no attempt to incorporate the HESI tiered approach into the proposed rule. The Agency does indicate that they will consider the proposed tiered approach once the HESI work products are published. The Agency also indicates that in the future they will determine what revisions to existing testing guidelines and data requirements may be appropriate and those changes will be made, as needed, to keep the data requirements current.

CLA submits that a significant opportunity exists to open a stakeholder dialogue now in regard to the proposals made in the HESI project, rather than at some future point in time. Such a dialogue clearly could build upon the existing international scientific consensus reflected in the HESI proposed tiered approach for testing of agricultural chemicals. We believe a number of the concepts developed there are ripe for incorporation into pesticide testing requirements at this time. Therefore, CLA requests that the proposed rule not be finalized until there is an opportunity to consider and incorporate the important concepts developed by the HESI project “Developing Strategies for Agricultural Safety Assessment.”

Subchronic Testing (dermal and inhalation toxicity studies)

General Comments [§158.500]

The table of toxicology data requirements is differentiated by use patterns defined as food and nonfood use patterns. This differentiation is based on the application of the toxicology data to dietary exposure and risk assessments. For the overwhelming majority of toxicity data requirements the differentiation based on food and nonfood uses is logical. However, the dermal and inhalation toxicity studies are not used for dietary risk assessment purposes. These studies are applicable to non-dietary risk assessments for handlers, field workers, and residential users. CLA proposes that the 21/28 day dermal (870.3200), the 90-day dermal (870.3250), and the 90-day inhalation (870.3465) data requirements be based instead on short-term or intermediate-term use patterns, possibly in a separate table. In addition, the requirement of a 21/28-day dermal

study should also be based on the Tier 1 risk assessment. If the dermal exposure is low, based on formulation type, use pattern, and exposure potential, additional studies and dermal data requirements would not be warranted. The frequency and duration of exposures associated with the use pattern are more relevant than whether the pesticide is applied to food crops or used for nonfood situations. For example, the data requirement tables for Subdivisions K and U differentiate use patterns based on occupational and residential uses. Occupational uses typically are both short-term and intermediate-term durations and residential use patterns are typically short-term duration. Therefore, designing the dermal and inhalation toxicity studies on the product's duration of use will make the data requirements consistent with the exposure assessment practices within the Agency and consistent with the data requirement for Subdivisions K and U.

Dermal Toxicity Testing

The proposed changes to Subdivision F include a 21/28-day dermal toxicity study requirement for food-use pesticides. This represents a change from the current conditional requirement. For non-food uses a 90-day dermal toxicity study would be required. The Agency states that if the major route of exposure for nonfood uses is the dermal route, the 21/28-day dermal toxicity study is insufficient to identify potential hazards. However, no justification was provided to support this assumption. CLA believes there is no basis for this statement. For example, many pesticide residential use patterns involve a single application or several intermittent applications during the year. A 90-day dermal toxicity study would not be relevant to such a use. The overwhelming majority of Agency assessments of operator and post-application exposure conclude that exposures to any active ingredient occur as intermittent events rarely exceeding a 45-day period. Therefore, the relevance of a 90-day dermal study is questionable for almost all nonfood and food uses. In addition, CLA doubts whether significantly different toxicological end points (e.g., NOAELs or target organs) would be generated in a 28-day versus a 90-day dermal study. Considering the low dermal absorption of many active ingredients, only minimal toxicity is typically observed in repeated dermal-exposure studies. These studies often are not used in risk assessments due to the lack of a relevant toxicity endpoint. A 28-day study should be considered sufficient for patterns involving short-term exposures occurring on an intermittent basis. The data from these studies, especially if conducted according to OPPTS Guideline 870.3200, should be sufficient in assessing potential systemic toxicity. If a 90-day dermal study is needed for risk assessment and a 90-day oral study is available (e.g., Guideline 870.3100), either dermal penetration data [Guideline 870.7600] or comparison of LOAELs from repeated oral studies [e.g., 28-day oral-OECD 407; 90-day oral Guideline 870.3100] and the 28-day dermal study could serve to extrapolate from an oral to dermal exposure scenario.

EPA is proposing for both food and non-food uses dermal testing on the end-use product, if the product or any component in it could lead to potentially toxic effects or could possibly increase the dermal absorption of the active ingredient. CLA requests that additional guidance is added to define those co-formulants and their contents in the end-use product that are considered likely to increase dermal absorption of the active ingredient.

Inhalation Toxicity Testing

The proposed rule would require the 90-day inhalation toxicity study conditional on the likelihood of significant repeated inhalation exposure to the pesticide as a gas, vapor, or aerosol.

The requirement for the 90-day study can also be shortened based on the magnitude and duration of human exposure. CLA is in general agreement with the principles and concepts laid forth in the data requirements, but is concerned that in practice the Agency will continue to require the 21/28-day or 90-day inhalation toxicity studies regardless of the method of pesticide application and the nature of the spray droplets to which an individual is exposed. An evaluation of recent REDs shows that this conditional requirement is being triggered by the Agency for most occupational use patterns. The Agency should clearly define the nature of the aerosol requirement to differentiate it from typical spray droplet particle sizes that are too large for inhalation into the lower respiratory tract. The inhalation toxicity study should be conditionally required for highly volatile products or products applied as a fine mist without the use of respiratory protection.

Summary Comments:

1. CLA proposes that the toxicology data requirement for the 21/28-day dermal, 90-day dermal, and 90-day inhalation toxicity studies be placed in a separate table that differentiates the data requirements based on occupational and residential use patterns rather than the dietary-based food- and nonfood-use patterns.
2. CLA proposes that the basic requirement should be a 21/28-day dermal study, conditional on the potential for significant and repeated dermal exposures and the overall toxicity profile of the active ingredient. If the toxicity endpoint selected for risk assessment is not determinable by a dermal toxicity study, then it should be waived.
3. CLA supports the “conditionally required” status for inhalation data, but is concerned that the Agency will make it a *de facto* requirement in the future. The need for this study should be based on the type of use and likelihood of exposure to respirable particle sizes. CLA recommends that improvements in technology for precise application methods and use of protective personal safety equipment be considered when imposing inhalation exposure data requirements.

Chronic Testing

The propose rule would change the name of “oncogenicity” studies to “carcinogenicity” studies. The term “oncogenicity” should be retained. Oncogenicity is a more general term referring to both benign and malignant tumors. The EPA guideline studies are designed to detect both tumor types. Carcinogenicity refers specifically to malignant tumors. The more general term “oncogenicity” should be used.

Non-rodent Testing [Unit XI.C.3.vi]

CLA supports the Agency’s proposal to eliminate the requirement for a 1-year dog study. As summarized in the background document (Baetcke, et al., 2005) for the May 5, 2005 Scientific Advisory Panel (SAP) meeting, retrospective comparisons in the literature and EPA’s own comparison demonstrate that for the majority of compounds, a single study in dogs, 3 to 6 months in duration, is sufficient for hazard evaluation. EPA’s analysis examined in detail 77 of 116 the pesticides with chronic RfDs based on dog data. In EPA’s view, there were indications for only 3 of the 77 pesticides that a dog study longer than 3 months was necessary. Thus, for most pesticides, extending the dog study to one year provides essentially no additional useful

information for risk assessment purposes. These examples were taken from a total of 304 pesticides, of which more than 60% have a chronic RfD based on a species other than dog. Although the SAP criticized EPA for not examining more of the 304 pesticides, the comparison of NOAELs in the dog becomes a moot point, as dog data were not used in risk assessment for 188 of the compounds due to another species being deemed as either more appropriate or more sensitive. When the 74 compounds for which EPA considered that a one-year dog was not necessary are included, the 90-day dog study is sufficient in 86% of the cases (i.e. $(188+74)/304$). This percentage would likely have been above 90% if EPA had evaluated all 116 pesticides with chronic RfDs based on dog data.

EPA's conclusion is also supported by an analysis performed by ILSI's Health and Environmental Sciences Institute (HESI) Technical Committee on Agricultural Chemical Safety Assessment (ACSA). NOAELs in the one-year dog studies were equivalent or greater than 90-day NOAELs for 65% of 26 pesticides evaluated. Of the remainder, approximately two-thirds had NOAELs comparable to or greater than NOAELs in the 2-year rat study. ACSA recommended that a 90-day dog study serve to identify potential species differences but that a study of longer duration could not be justified. ACSA also recommended that if greater sensitivity was observed in the dog than in the rat, consideration should be given to using an additional uncertainty factor in risk assessment.

In assessing toxicity, the proportion of the test animal's life span represented in a study should also be evaluated in determining the usefulness and interpretation of results. One year represents 8% a Dog's average 12-year life span, while 90 days constitutes 2%. The difference is not significant enough to consistently provide additional information truly useful for risk assessment. EPA's analysis supports that little new information is obtained through testing over very similar proportions of an animal's lifespan.

Considering these details, it is difficult to justify the continued requirement for both studies from the perspectives of toxicology and animal rights. Assuming 32 to 48 dogs are used in each one-year study, eliminating this redundant study would have resulted in some 9,000 to 15,000 fewer dogs being used in testing the 304 compounds.

Neurotoxicity Testing [Unit XI.C.2.ii and §158.500]

Proposed Revision: "The Agency believes that the current set of neurotoxicity studies are inadequate for some chemicals in their observation of behavioral effects and do not use optimal methods to evaluate the nervous tissue structure and function. To detect and characterize these potential effects more fully in certain chemicals, a battery of more sensitive testing would be required. Several neurotoxicity studies are proposed to be added to the already existing neurotoxicity study requirements for all conventional pesticide registrations. The objective of the new acute and subchronic battery is to evaluate the incidence and severity of the functional and/or behavioral effects, the level of motor activity, and the histopathology of the nervous system following exposure to a pesticide. A new adult neurotoxicity test battery of seven studies would replace the current adult neurotoxicity test requirements."

These seven tests would include studies of acute and a subchronic (90-day) neurotoxicity in rats (Guideline 870.6200), delayed (28-day) neurotoxicity in hens (Guideline 870.6100), scheduled

controlled operant behavior (Guideline 870.6500), peripheral nerve function (Guideline 870.6850), and sensory evoked potential neurophysiology (Guideline 870.6855).

CLA Comment: EPA must be more transparent about their basis for concluding that the current set of neurotoxicity studies is inadequate. Over the past 15 years, Industry has spent millions of dollars and used thousands of animals generating neurotoxicity data according to the study design in OPPTS guideline 870.6200. Any analysis of those studies, which has led EPA to consider them inadequate, should be made publicly available for scientific discussion.

CLA agrees with the requirement for an acute neurotoxicity study. However, we believe that a subchronic neurotoxicity study should be conditionally required based on consistent evidence of neurotoxicity in other studies, a mechanism of pesticidal action related to nervous system function, or structural similarity to neurotoxic compounds.

CLA agrees with the conditional requirement of a 28-day delayed neurotoxicity study in hens, with the understanding that this requirement would apply only to organophosphate compounds. For clarity, EPA should specify in the text that a 28-day study in hens is triggered only by the results of an acute study in hens, as clearly stated in test note 15. In the table of toxicology requirements, note 6 for the acute study in hens should also be added to the 28-day hen study. CLA agrees that a study duration of 28 days in hens is sufficient to evaluate the potential for delayed neurotoxicity.

CLA has two concerns that pertain to the three specialized neurotoxicity studies (Guidelines 870.6500, 870.6850, and 870.6855). First, to our knowledge, these study designs have never undergone an inter-laboratory validation using blind positive and negative reference compounds. Experience gained through a validation process would be critical to interpreting the outcome of these tests correctly and understanding the biological significance. None of these three study types should be requested until such a validation process has been performed with satisfactory results, as we should not re-create the current situation faced with the DNT study. After having generated DNT data over the past 15 years, it is only now that an ILSI group has been formed to evaluate the DNT study design and interpretation. Although we support the efforts of this group, this step after 15 years of data generation implies that the Agency has been requesting a study without having sufficient knowledge to understand or to interpret the biological significance of the data generated. This step should be part of validation of the reliability and sensitivity of any study design, prior to its use in a regulatory setting.

Second, once the tests are validated, clear triggers should be established for when these tests would be necessary. One of the main concerns about the proposed rule as written is a lack of specificity for triggering criteria. EPA proposes for registrants to conduct these studies if the acute and/or the subchronic neurotoxicity studies in rats show “adverse effects on the central nervous system which affect learning, memory or performance, or adverse effects on visual, auditory, or somatosensory senses and/or concerns for peripheral neuropathy.” Other triggers cited for these three studies are “structure activity considerations or to more fully characterize any neurotoxic effects seen in the acute and subchronic studies.” The basis for EPA’s conclusion that these tests would rarely be required is not provided. In our experience with EPA’s interpretation of data from neurotoxicity studies, the trigger criteria are sufficiently generalized

that almost any statistical change, even in the absence of biological significance or a dose-response, would result in triggering these studies. The indication that a scheduled controlled operant behavior study could be required simply based on evidence of CNS depression or stimulation suggests that a clinical observation of hypo- or hyperactivity could be considered sufficient evidence. Likewise, it is inappropriate to require peripheral nerve function testing based on the presence of a CNS lesion without a consistent pattern of effects. A transient decrease in response to sensory testing in a functional observational battery is also not an adequate trigger for a test of evoked potential. In addition, more clarification is needed as to which neurotoxicity studies would be required if a pesticide was structurally similar to a neurotoxicant. CLA believes that specific and scientifically justifiable triggers are needed for EPA to require any of these three neurotoxicity studies. It is common for animals to be hypoactive after a single high dose; this may be a sign of systemic toxicity and not due to neurotoxicity.

Finally, the proposed revision refers to guideline 870.6855 as “sensory evoked potential neuropathology” while the published guideline is entitled “Neurophysiology: sensory evoked potential”. Terminology in the revised Part 158 should be consistent with current guideline titles.

Reproductive Toxicity Testing [Unit XI.C.3.v and §158.500]

The proposed tiered testing scheme (second option) for nonfood-use pesticides lists the DNT as part of the first-tiered, required testing (Part 158.10). This is inconsistent with the test requirements recommended for food-use pesticides, in which the DNT is a conditional requirement triggered by a weight-of-the-evidence approach from existing data (see Part 158.500; test notes 26 and 27). CLA recommends that the DNT be moved to the conditionally required second-tier studies for non-food use pesticides.

Test Note 25

The draft suggests combining the rat developmental toxicity study with the two-generation reproductive-toxicity study. Some of the technical and logistical challenges arising from this recommendation, which limit the utility of this approach include the following:

- Any compound-related effects on mating success, fertility, or fecundity will limit the number of litters available for evaluation.
- Information on early post-implantation loss will be missing (for both the reproductive toxicity study used for the combined approach and the developmental toxicity evaluation), as it is not possible to determine at necropsy which implantation scars in the dams resulted from which pregnancy.
- Pre-implantation loss may be increased due to exposure starting at the time of conception, rather than at the time of organogenesis, limiting the ability to discern teratogenicity.
- Laboratories will not be able to rely on their historical database for developmental toxicity studies to assist in determining the treatment-relationship of equivocal findings. The differences in timing of exposure and use of litters from time mated (currently used

in many laboratories) versus naturally mated dams are likely sufficient to preclude comparison of data from the modified combined study design with the control data from standard Part 158 Guideline developmental toxicity studies.

Test Note 28

Combining the reproductive toxicity studies with developmental neurotoxicity (DNT), as suggested in test note 28, while laudable on grounds of animal protection and efficiency, poses a number of important technical and logistical challenges that may potentially diminish the utility of data from one or both of these studies. (Note that in test note 25, it is also suggested that the rat developmental toxicity study be combined with one generation of the two-generation reproductive toxicity study; some of the same problems may be seen as discussed above).

The two-generation study currently serves as one of the studies used as a screen for triggering a DNT. It provides a unique opportunity for observation of pup behavior. EPA should complete its evaluation of the DNT data compared to data from the two-generation study to determine how frequently a DNT study actually provides a lower NOEL for risk assessment, before requiring either a separate DNT study or combined reproductive toxicity and DNT study. Beyond this, there are several specific problems that merit attention.

- The two-generation reproductive toxicity study frequently serves as a range-finding study for a DNT, to assure that an MTD for pups has not been exceeded. The rat developmental study frequently serves to provide data for maternal dose selection for a DNT. Combining either the rat developmental toxicity study or the DNT with the reproductive toxicity study would require a longer and greater animal-intensive range-finding study to ensure that the proposed doses to the maternal animals and pups are not excessive, and to help predict a NOAEL for the pups. Lacking adequate perinatal data to assist in dose selection, results from a DNT are likely to be flawed or not meet Guideline requirements. Some of the ‘savings’ in animals and efficiencies would be lost due to this need for an extended and larger-scale range-finding study.
- The most appropriate route of administration may not be the same for both studies, therefore it may not be possible to combine them.
- As noted above, using pups from the second pairing of a generation will inevitably result in the loss of important reproductive toxicity data from that generation. In particular, information on early post-implantation loss will be missing.
- Frequently a second pairing results in lower fecundity, with fewer pups available for evaluation. A DNT study requires large litters to permit allocation to the various tests required, particularly if additional endpoints requiring pup sacrifice, e.g., cholinesterase determinations, are necessary to provide either a basis for a NOAEL or a basis for establishing exposure to the pups. Thus larger numbers of parental animals would have to be used to ensure sufficient numbers of litters and pups for all tests. Using more than one offspring from one litter for a particular test as an alternative to larger group sizes introduces large litter effects, which may confound interpretation of the DNT results.

- The likelihood of too few pups for evaluation is likely to be exacerbated by the exposure from the time of conception, which may increase pre-implantation loss. The proposed rule cites exposure from the time of conception as an advantage, but it is equally likely to prove a handicap, unless the current requirement for the high dose to produce clear evidence of maternal toxicity is modified.
- A combined protocol is not in-line with efforts to harmonize international testing requirements and use of such a design may compromise international acceptability.

Last, but most importantly, the immense logistical complexity of the combined study design with increased numbers of animals, a longer duration, and multiple parameters for evaluation is likely to result in increased laboratory error and increased variability primarily related to technician “burn-out.” A combined approach is more likely to be feasible if the number of parameters required for each study type is reduced, which may be possible through focusing on endpoints that have provided driving effects for hazard assessment in the reproductive and DNT studies currently available to the Agency.

Tiered Testing Options for Nonfood Pesticides (§158.510)

There is a flaw in the proposed tiered testing scheme (second option) for non-food use chemicals. The required first-tier studies include a two-generation reproductive toxicity study. We believe that the tiered testing scheme would be most efficient if the two-generation reproductive toxicity study were a conditional second- or third-tier test requirement for non-food use chemicals, and that it is logical to require this study based on evidence of exposure.

Developmental neurotoxicity (DNT) Testing [Unit XI.C.2.iii and §158.500]

The Agency proposes that developmental neurotoxicity testing be conditionally required for conventional food use and nonfood use pesticides.

CLA Comment: CLA agrees that the DNT study should be a conditional requirement, determined on a case-by-case basis. EPA provides a list of endpoints that could trigger a DNT study. These endpoints should not be used individually in isolation but should be used in combination to identify a pattern of effects indicative of potential developmental neurotoxicity. EPA should do a weight-of-the-evidence evaluation, with a DNT being triggered only if there is a consistent pattern of responses in several studies. Furthermore, effects observed at excessively toxic dose levels or at maximum tolerated doses where general nutrition and/or weight gain has been compromised should not trigger a DNT. For example, lower pup brain weights are frequently the result of significantly decreased body weight. Brain weight development is not completely conserved with decreased weight gain, and thus this endpoint alone should not be viewed as sufficient justification for requiring the DNT. Likewise, “clinical signs of neurotoxicity” may be an appropriate trigger for a DNT, but only if observed in non-moribund animals (i.e. not the result of near-lethal doses) in a dose-related fashion. However, clinical signs, such as tremors, observed sporadically in a small number of animals in a single study, provide insufficient evidence to trigger a DNT.

Further clarification is needed from EPA about “functional or behavior effects” in adult or developing animals which would trigger a DNT. In addition, EPA should provide definitions of

“altered” effects and “adverse” effects to differentiate between findings, which would or would not trigger a DNT. Finally, EPA must explain how they would interpret “altered neuroreceptor or neurotransmitter responses” for the purposes of triggering a DNT. Careful consideration should be given to any mechanistic data, such as neuroreceptor response, and should include relevance of doses tested, route of administration, and robustness of data set prior to using these studies as a DNT trigger.

The option of substituting a DNT study with a more targeted assay requires a thorough understanding of the endpoint selected. Although a relative sensitivity study is simplistic in design, the significance of the results cannot be entirely understood without supporting pharmacokinetic and pharmacodynamic data. Also, knowledge of underlying biochemical and physiological differences between neonates and adults is critical to understanding the toxicological significance of any findings. Identifying an appropriate, quantifiable endpoint is likely to be problematic for many classes of chemistry. Further, the relevance of direct dosing in animals considered to represent the pre-term human infant/fetus is questionable in risk assessment. The kinetic disposition of a bolus dose is likely to be considerably different for most compounds than more gradual exposure received via milk or food.

CLA is concerned that, after having generated DNT data over the past 15 years, an ILSI group has been only recently formed to evaluate the DNT study design and data interpretation. This step should be part of an up-front validation of the reliability and sensitivity of any study design. Although we support the efforts of this ILSI group, this step after 15 years of data generation implies that EPA has been requesting a study without having sufficient knowledge to understand or to interpret the biological significance of the data generated. In our view, a similar situation is being created with relative sensitivity studies and the three specialized neurotoxicity studies to assess scheduled controlled operant behavior (guideline 870.6500), peripheral nerve function (guideline 870.6850), and sensory evoked potential neuropathology (guideline 870.6855).

CLA supports the option to combine tests whenever feasible. This suggestion is consistent with many of the proposals from ILSI’s Health and Environmental Sciences Institute (HESI) Technical Committee on Agricultural Chemical Safety Assessment (ACSA). Combining a DNT study into a reproduction study should be technically feasible, but the problems noted above in the reproduction section would need to be addressed. In addition, combination of the DNT and reproduction study may require using a lower high dose than might be tested in the reproduction study design described by guideline 870.3800. The stated criteria for high dose selection in the reproduction study are “...to induce some reproductive and/or systemic toxicity but not death or severe suffering.” Frequently this dose level causes systemic toxicity in pups sufficient to confound interpretation of a developmental neurotoxicity evaluation. Consideration should be given to adjusting dietary levels during lactation to maintain a reasonably constant dose throughout the study and to reduce the possibility of pups receiving an overtly toxic dose when they begin to eat the diet during the last week of lactation. Another difficulty is that the DNT study basically becomes a requirement rather than a conditional study. Therefore, the option to conduct two separate studies needs to be retained.

Finally, CLA notes that Guideline 870.6300 does not reflect modifications the EPA has required in the study design in recent years. For example, the guideline requires brain weights and neuropathology on postnatal day 11 pups, but in reality, EPA requires these assessments on postnatal day 22 pups. This guideline should be updated to reflect the study design currently being required by EPA.

Mutagenicity Testing [Unit XI.C.2.iv and §158.500]

EPA has proposed changing the specific types of tests that are submitted to satisfy the requirement for evaluating the mutagenic potential of pesticide products. The new initial battery of tests will consist of a bacterial gene mutation assay with *Salmonella typhimurium* and *Escherichia coli* (Guideline OPPTS 870.5100); an assay in mammalian cells in culture (either a mouse lymphoma assay or the combination of a CHO or V79 HGPRT assay accompanied by an *in vitro* test for clastogenicity; guideline OPPTS 870.5300 and 870.5375); and an *in vivo* cytogenetics assay (guideline OPPTS 870.5385 or 870.5395).

Comment: CLA agrees with EPA that it is appropriate to update the initial battery of mutagenicity studies to reflect continuing developments in the field of genetic toxicology testing. The battery proposed by the Agency is consistent with that published by OPP in 1991 (EPA 540/09-91-122, NTIS Publication No. PB91-158394, Dearfield et al., Mutation Research 258:259-283, which has formed the basis of the current genetic toxicology requirements for pesticide registrations for the last 14 years.

More recently EPA personnel (Dearfield, et al., 2002, Mutation Research 521:121-135) have reconsidered the initial mutagenicity testing battery, again taking into account further developments in the field, as well as increasing concerns regarding animal use in toxicological testing. A four-tiered testing approach is now suggested, beginning with an initial battery of three *in vitro* mutagenicity studies – a bacterial gene mutation test (OPPTS 870.5100), an *in vitro* gene mutation test in mammalian cells (OPPTS 870.5300), and an *in vitro* chromosome aberration test (OPPTS.5375) with scoring for numerical and structural aberrations. Testing for genotoxicity in somatic cells of animals (Tier 2) is triggered by the results of Tier 1 and by “high or moderate and prolonged levels of exposure.” If the three *in vitro* tests are uniformly negative, the authors contend that this will “provide sufficient information for the assessment of most substances.” The overall presumption is that a substance lacking the capacity to induce genotoxic damage *in vitro* is unlikely to be an *in vivo* mutagen. If one or more *in vitro* tests produce positive results, then the *in vivo* cytogenetics test (*in vivo* chromosome aberration or micronucleus) is required and possibly a second *in vivo* test in another tissue. The selection of a second *in vivo* somatic cell study is made on a case-by-case basis taking into account factors such as chemical structure of the compound; metabolism and toxic kinetics; data on analogs or its metabolites; and the results of the three *in vitro* mutagenicity studies. If a substance is genotoxic in somatic cells of animals, additional testing at Tier 3 for interaction with gonadal DNA and possibly Tier 4 for transmission of heritable mutations to offspring would be considered.

CLA encourages the Agency, during the process of updating and revising the Part 158 data requirements, to take into account the latest mutagenicity testing proposal made by its own experts. The proposed three-test initial battery is attractive, as it not only minimizes animal use

in the mutagenicity testing of substances negative for genotoxicity *in vitro*, but is consistent with actions by other national authorities to streamline the initial battery of mutagenicity studies [e.g., UK Committee on Mutagenicity of Chemicals in Food, Consumer Products, and the Environment (COM), “Guidance on a strategy for testing of chemicals for mutagenicity”, Department of Health, 2000; Ministry of Agriculture, Forestry and Fisheries (MAFF), Japan, 2000]. Adopting a three-test *in vitro* screening battery, however, requires clarification by EPA of when *in vivo* somatic cell studies may be required and the selection of those studies. For instance:

- What are the criteria for high or moderately prolonged exposure that would trigger *in vivo* testing as part of the initial tier of studies, if the three *in vitro* mutagenicity studies are negative, and these studies are determined to have met the criteria for valid studies?
- Is a second *in vivo* genotoxicity study (e.g., *in vivo* hepatocytes UDS) necessary if the *in vitro* chromosome aberration study is the only *in vitro* test producing a positive response and negative results are obtained in an adequately conducted *in vivo* cytogenetics test?
- In the event that the *in vitro* mammalian-cell gene-mutation assay produces positive results, which *in vivo* study(s) does the Agency consider appropriate?

In 1991, the rationale for further testing beyond the initial mutagenicity battery, including studies in germ cells, was provided in EPA’s NTIS Publication No. PB91-158394/AS and has been addressed more recently by members of the Agency in a publication by Dearfield et al., 2002. Clearly, decisions to proceed with further mutagenicity testing will need to be made on a case-by-case basis, taking into account the overall weight of the evidence for mutagenic risk. However, the rationale for higher-tiered testing and the accompanying recommended studies are not included in the current Part 158 data requirements or in the proposed revisions. In order to consolidate available guidance and to provide the current requirements of the Agency, CLA encourages EPA to outline the typical triggers for proceeding with subsequent *in vivo* somatic and germ cell studies and examples of the types of tests that EPA considers appropriate.

Dermal Penetration Testing [§158.500]

The dermal penetration study is listed as a Conditional Requirement for both food and nonfood uses. The test substance is listed as “choice” between a manufacturing product and an end-use product. Test note no. 34, which refers to the dermal penetration study states:

“Required if toxic effects are identified in the oral or inhalation study. A risk assessment assuming that dermal absorption is equal to oral absorption must be performed to determine if the study is required, and to identify the doses and duration of exposure for which dermal absorption is to be quantified.”

Comment: The OPPTS Guideline for dermal penetration (OPPTS 870.7600) is excessive in the number of time points evaluated and the number of animals used. Three or four dose levels with three to six exposure periods and the use of 12-24 animals [per dose level/time period combination?] is recommended. CLA strongly suggests that a more abbreviated guideline be developed, e.g., similar to OECD 427.

OECD Guideline 427 does not set a specific number of dose levels, recommends fewer exposure periods, and consequently requires the use of fewer animals. In an effort to reduce the number of animals used in testing and still gather sufficient data to determine the dermal penetration potential of chemicals, the OECD protocol is more appropriate than the current OPPTS guideline. For risk assessment purposes, the endpoint of interest is the percentage of applied material that penetrates the skin. A single contact period (e.g. 6-8 hours) that mimics potential human exposure is sufficient. Only two concentrations are typically needed, the undiluted formulation and the dilute (spray) concentration, which represent exposures during mixing and loading and during application. Dermal penetration can be determined at the end of the contact period (e.g., 6-8 hours) and one additional time point (e.g. 72 or 168 hours). The latter sampling time point allows quantification of skin (e.g., stratum corneum) residues available for continued absorption over time. Whether or not to add this amount to the systemically absorbed dose can then be determined.

A calculated dermal penetration percentage should be accepted in lieu of a dermal penetration study. The Agency has been inconsistent in its acceptance of this calculation method. The LOAELs from repeat-dose oral and dermal studies can be compared. The dermal penetration is calculated by: (oral LOAEL)/(dermal LOAEL). This gives an approximate dermal penetration percentage. If a risk assessment is not acceptable using this calculated value then a specific *in vivo* dermal penetration study can be performed to determine a more specific value.

Various percutaneous absorption studies have shown that rat skin is typically 2-10 times more permeable than human skin. (Bartek, et al 1972; Lockley et al, 2002; Moss et al, 2000; van Ravenzwaay and Leibold, 2004). Therefore, an *in vivo* study conducted in rats may overestimate human dermal penetration potential. The OECD accepts the use of an *in vitro* rat-to-human comparison study (OECD Guideline 428) to adjust the rat *in vivo* results, as appropriate. OPP does not currently accept the *in vitro* method.

The use of the comparative (rat to human) *in vitro* dermal penetration data in combination with the rat *in vivo* data will allow a more accurate determination of human dermal penetration. CLA requests that OPP review the OECD *in vitro* comparative dermal penetration protocols that are available and develop an OPPTS guideline for this study. It is interesting to note that for TSCA regulated chemicals, the EPA has proposed *in vitro* dermal penetration studies (Federal Register vol. 64, no. 110, page 31074).

Test note 34 indicates that the dermal penetration study is required if toxic effects are identified in the oral or inhalation study. If all oral and inhalation studies are considered, then a toxic finding would almost always be guaranteed, because the guidelines require testing to a toxic dose. This point needs clarification.

CLA agrees (as stated in test note 34) that the determination of the need for a dermal penetration study should be made after a risk assessment is performed to determine if the assumption that dermal absorption is equal to oral absorption allows for an acceptable risk to be determined. If that fails, a stepwise approach should be used and not automatically require an *in vivo* dermal penetration study.

A step-wise approach would include several steps. If an acceptable risk assessment can be obtained from the assumption that dermal penetration is equal to oral absorption, then a dermal penetration study is not needed. If the risk assessment is not acceptable then a calculation of the dermal penetration can be made comparing LOAELs from repeat-dose oral and dermal studies (as mentioned above). . If an acceptable risk is still not obtained, then a human *in vitro* dermal penetration study is performed. If that does not lead to acceptable risk, then an *in vitro* and *in vivo* rat dermal comparison study is conducted and a human dermal-penetration value is calculated. European regulators currently utilize this tiered approach to assess dermal penetration. The European guidance (SCP 2002) is to first use *in vitro* dermal penetration in human skin. If this is not adequate, refinement would be to use *in vitro* and *in vivo* rat to correct for projected *in vivo* human dermal penetration. Because many products are developed for global markets, an *in vitro* dermal penetration study may be available. CLA recommends that EPA accept these data as part of the first-tier exposure and risk assessment process. If this first-tiered approach demonstrates acceptable risk, there is no need to conduct an *in vivo* dermal penetration study as now conditionally required by the Agency. This would prevent needless use of animals and provide a satisfactory risk assessment.

References:

Bartek, J.J., Labuddle, J.A. and Maibach, H. I. (1972) Skin permeability in vivo: Comparison in rat, rabbit, pig and man. *J. Invest. Dermatol*, 58: 114-123.

Lockley, D.J., Howes, D. and Williams, F.M. (2002) Percutaneous penetration and metabolism of 2-ethoxyethanol. *Toxicol. Appl. Pharmacol.* 180 (2):74-82.

Moss, T, Howes D. and Williams, F.M. (2000) Percutaneous penetration and dermal metabolism of triclosan (2,4,4'-trichloro-2'-hydroxydiphenyl ether). *Food Chem. Toxicol.* 38(4):361-370.

Van Ravenzwaay, G. and Leibold, W. (2004) A comparison between *in vitro* rat and human and *in vivo* rat skin absorption studies. *Hum. Exp. Toxicol.* 23(9): 421-430.

Immunotoxicity Testing [Unit XI.C.1 and §158.500]

Immunotoxicity testing is a newly imposed requirement for all chemical pesticides, food use and non-food use. Testing should be conducted in accordance with the harmonized Health Effects Test Guidelines for Immunotoxicity (OPPTS 870.7800) published in 1998. As many companies have been practicing the essentials of this test guideline on a “voluntary” basis, there are no general comments on the requirement of functional immunotoxicity data for chemical pesticides. However, in light of the updated data requirements, further review of the 1998 OPPTS 870.7800 Immunotoxicity Test Guideline raises a number of issues.

- 1) The primary functional assay prescribed by OPPTS 870.7800 is the Sheep Red Blood Cell (SRBC) Antibody Response following exposure to test (and control) materials for at least a 28-day period as appropriate for the testing protocol for a specific route of exposure.

OPPTS 870.7800 should be updated to allow use of alternate antigens (e.g., KLH) that have been effectively used to evaluate the antibody response in laboratory rodents, since the Guideline was

published in 1998. Data generated using alternate antigens should be considered acceptable if its validity and sensitivity as compared to that of the SRBC protocols are demonstrated.

- 2) In the event that the test material produces a suppressed antibody response, expression of lymphocyte surface antigens (via flow cytometry) may be evaluated to further characterize a dysfunctional immune response. Alternatively, if the test substance has no significant effect on the primary antibody response, the testing guideline indicates that a functional test for NK cells may be conducted to assess non-specific immunity.

The rationale for requesting additional immunotoxicity data is ill defined by the test guideline. The ultimate decision should incorporate a weight-of-evidence approach, taking into consideration many aspects of the product safety assessment. For classification of a chemical as an immunotoxicant, the conduct of flow cytometry is likely to be academic in nature (i.e., identifying the target cell(s) will not change the immunotoxicant classification). Depending upon a laboratory's SRBC study design, it would also require additional animals to address such a question. We expect that a decision to conduct flow cytometry under the conditions outlined in the test guideline can be discussed with the Agency, but will be performed at the discretion of a pesticide registrant. Furthermore, while the NK assay is designed to measure the innate immune response, there is a lack of data to support chemicals eliciting suppressed NK activity in the absence of altering the coordinated, adaptive antibody response. A combination of negative results from endpoints such as WBC differentials, immune organ pathology, and the primary antibody response might preclude the need to perform the NK Assay, and prevent the unnecessary use of animals. In addition, appropriate NK assay protocols have not been specifically defined or validated; thus, it is expected that there will be some leeway regarding study design based upon measured responses using positive controls.

Therefore, dialog and a weight of evidence approach, similar to that proposed in the Draft Consensus Guideline, Immunotoxicology Studies for Human Pharmaceuticals by ICH S8 (Nov 2004; www.fda.gov/cder/guidance/6636dft.doc), which incorporates other studies (e.g., 28- or 90-day general toxicology studies) and endpoints, should be used to determine the necessity for conducting an NK Assay or other immunotoxicological endpoints.

- 3) The proposed rule encourages combined study protocols and has new emphasis on tests using developing (young) animals. In addition, there have been a number of open scientific forums in which study designs that evaluate immune function following critical exposure periods have been generally agreed upon [e.g., Holsapple et al. 2004. A proposed testing framework for Developmental Immunotoxicology (DIT). *Tox. Sci.* 83(1): 18-24]. Currently, there are no provisions in OPPTS 870.7800 to conduct a guideline immunotoxicity study in accordance with peer-reviewed proposals for developing rodents.

Until specific DIT Test Guidelines are validated and published it is anticipated that open dialog will occur with Agency scientists to design "life stage immunotoxicity" evaluations using the rationale mentioned above and consistent with the peer-reviewed state of the science.

Subpart J - Nontarget Plants

The series 850 guidelines should be finalized before the Part 158 data requirements are finalized. It is difficult to comment on the Part 158 data requirements when the studies referenced are still in draft form and may be subject to significant change. CLA requests that EPA not finalize any data requirements until final guidelines are available.

Seed Germination (Preamble Unit XII.B, p. 12298d)

CLA supports elimination of seed germination as a nontarget plant (NTP) study endpoint. Potential adverse impact to NTPs from compounds that could have a primary impact on seed germination, such as soil fumigants or a new family of herbicides, would be quantified through reduced emergence in the seedling emergence study.

Seedling Emergence and Vegetative Vigor (Guidelines 850.4100 and 850.4150)

The proposed rule would require a TEP (typical end-use product) as the test substance (rather than TGAI (technical grade active ingredient)) for the seedling emergence and vegetative vigor studies. This revision is in line with the current OPPTS guidelines and current Agency practice. We would recommend, however, that the TEP be the preferred test substance, with an option of using a different formulation or the TGAI, if there are difficulties related to use of the TEP for these studies. For example, in some cases the TEP may be a mixture of two or more active ingredients. However, adverse impacts on plants must be assessed separately for individual active ingredients. In this case it would be necessary to modify the TEP to include only a single active ingredient or use the TGAI rather than the TEP in order to obtain data on a single active ingredient. Additionally, for products that are in development at the time NTP testing is conducted, it is possible that the formulation may be further refined before the product is marketed. In such a case, the test material for NTP tests may not be identical to the commercial TEP, but should nevertheless be acceptable.

CLA supports use of the TEP containing the highest concentration of active ingredient or similar representative formulation in the seedling emergence and vegetative vigor studies.

CLA agrees that it is appropriate not to require vegetative vigor studies for granular or bait formulations.

We note that OECD is currently considering draft guidelines for seedling emergence and vegetative vigor studies. We encourage EPA to collaborate with OECD in harmonizing their respective guidelines for these studies, so that registrants can avoid unnecessary duplication of effort in supporting registration actions in different countries.

Aquatic Plant Growth (Guidelines 850.4400 and 850.5400)

CLA recommends that the testing of 5 species of aquatic algae and plants should not be required for non-herbicides. The need for additional testing of other species should be based on the LC50 values of the two species tested and the EEC. This should be clarified in the test notes for this subpart.

Tier III Studies (Guidelines 850.4300 and 850.4450)

The proposed rule would “require independent laboratory validation [ILV] of the environmental chemistry methods used to generate data associated with [Tier III] studies”. The ILV requirement is currently limited to methods for quantifying residues in food, soil, water and air. The proposed revision does not state which additional matrices are to be addressed nor how the ILV would be used. The requirement for ILVs would add an additional burden to the registrants if ILVs are required for the spray mixture or other matrices for which there are no current ILV requirements. We recommend that the proposed requirement be clarified to accept ILV conducted to meet similar requirements under Subparts N or O for residue chemistry and environmental fate. Thus, the need for additional ILV of methods for these Tier III studies should be rare.

Following a process of problem formulation and confirmation of ecologically relevant endpoints, the Tier III study guidelines should be revised as needed, both to insure that the studies are designed to produce information useful for refinement of ecological risk assessments and to provide guidance on practical, manageable approaches to conducting these studies.

Subpart K - Post-application Exposure

General Comment: The Agency lists among the data requirements Guidelines 875.2300 (indoor surface residue dissipation), 875.2700 (product use information), 875.2800 (description of human activity), and 875.3000 (nondietary ingestion exposure), which have not been finalized in the OPPTS Harmonized Test Guidelines for Occupational and Residential Exposure. (A rudimentary 1-page “final” guideline 875.2800 is posted at http://www.epa.gov/opptsfrs/OPPTS_Harmonized/875_Occupational_and_Residential_Exposure_Test_Guidelines/Series/875-2800.pdf, but a subsequent more detailed revision (<http://www.epa.gov/scipoly/sap/1998/march/chapb-12.pdf>) has not been finalized.) CLA disagrees with the imposition or codification into a federal regulation any data requirement that relies upon a reference guideline that does not officially exist. CLA also believes the Agency must finalize and issue revisions to the Series 875-Occupational and Residential Exposure Test Guidelines, Group B, which incorporates guidance on the conduct of indoor surface residue dissipation studies, prior to imposing data requirements for such studies.

Biological monitoring (Guideline 875.2600)

CLA supports the inclusion of biological monitoring (Guideline 875.2600) as a conditional data requirement. However, test note 12 (p. 12348c) states that human pharmacokinetic data for the active ingredient must allow back-calculation to the total internal dose. Unit XX of the Preamble on Research Involving Human Subjects (p. 12312c) specifically mentions biological monitoring studies as well as metabolism and pharmacokinetics. While CLA supports the use of human studies conducted under proper ethical guidelines, we recommend that the Agency allow flexibility in the development of supporting pharmacokinetic data, accepting also pharmacokinetic data from rodents or primates, with appropriate supporting rationale regarding their applicability to humans.

Description of human activity (Guideline 875.2800)

In addition to product use information, EPA has also proposed to require submission of information “describing the possible activities ... in which people may be engaged after a site has been treated” (i.e., post-application exposure scenarios). Such information would include the types of activities performed in treated areas; the timing, frequency, and duration of those activities; “principal source(s) of exposure”; possible mitigating factors; a “description of exposed population”; and other information. Although CLA agrees that this information is essential for accurate assessment of post-application exposure, there are several aspects of this requirement, as currently written, that appear to be problematic:

1. Several components of this requirement are vague to the point where it would be difficult to generate scientific information to specifically address the point (e.g., “description” of populations). Other components appear to pre-suppose what should be research data (e.g., “principal source(s) of exposure”). Still other components are very quantitative but would require significant research to know with precision. CLA believes the Agency has access to adequate information to fulfill this need through the ARTF Survey. However, the very significant time and resources that the ARTF Survey required show that the exact parameters of this data requirement will make the difference between whether only some expert

agronomic input is required, or whether a multi-million-dollar data collection project is required.

2. The importance of this data notwithstanding, it is noteworthy that these data are not necessarily product-specific, and may be considered the most “generic” of the proposed requirements. Only those data relevant to the assessment of a specific post-application scenario for a specific product are logical product-specific requirements. CLA believes this point should be clarified (along with items in #1 above) to make clear which specific requirement(s) would apply to a specific product.
3. ARTF has generated and submitted by far the most extensive and comprehensive survey of North American agricultural post-application exposure activities that has been performed to date, or is likely to be performed for some time to come. Agency Guidelines typically present a concise summary of major developments in relevant theory and research on the topic in question, thus, the ARTF Survey of North American Growers bears mention, even if only cited as a comprehensive source of information available to satisfy this data requirement.

Non-dietary ingestion exposure (Guideline 875.3000)

The Preamble states (p. 12301e) that this guideline would address behavior patterns, monitoring the amount of soil or residue from hand-washing, and developing science-based models or formulas to estimate inadvertent exposure. The ambiguity in the data requirement is evident in the following statement from the draft guidelines, Chapter 9, p. B9-5 (Series 875 - Occupational and Residential Exposure Test Guidelines. Group B - POSTAPPLICATION EXPOSURE MONITORING TEST GUIDELINES. Version 5.4. USEPA/OPPTS February 10, 1998. See <http://www.epa.gov/scipoly/sap/1998/march/contents.htm>):

Recently, EPA’s National Exposure Research Laboratory (NERL), Human Exposure and Atmospheric Sciences Division (HEASD) designed a program to explore the pediatric and behavioral science literature for activities such as hand-to-mouth or object-to-mouth activity that could be used to explain nondietary exposures (U.S. EPA, 1998a). Statistical prior or “premodel” distributions of activities were to be established based on demographic characteristics. These premodel distributions were to be tested in field studies at day care centers where the behavior of children could be both observed directly by experts and videotaped. These studies would be expected to produce a data base of “postmodel” distributions for certain patterns of behavior that could be studied under controlled laboratory conditions using adult human subjects to measure dermal contact and transfer of surface residues by whole-body dosimetry. The aim of the research was to reduce or eliminate the need for exposure studies that require human subject participation. U.S. EPA (1998a) summarized data taken from the open literature on the duration and extent of hand-to-mouth and object-to-mouth activity, sorted according to predictor variables. The predictor variables included factors such as age, sex, ethnicity, and socioeconomic status. The literature review demonstrated the relative importance of the factors impacting nondietary ingestion exposure. These data may be useful for assessing nondietary exposure from hand-to-mouth or object-to-mouth activity for the population of interest.

The Agency needs to provide details on the specific “developing science-based models and formulas” it has in mind.

Nondietary Exposure Methodology (Guideline 875.3000)

The proposed rule would impose data requirements for non-dietary ingestion before EPA has addressed the concerns raised by the Scientific Advisory Panel (SAP) in its most recent (1998) report concerning the proposed 875 Part B guidelines (see <http://www.epa.gov/scipoly/sap/1998/march/postapp.htm>). Hand residue data is a critical component of addressing non-dietary ingestion. However, in that report the SAP concluded that

... the guidelines do not adequately address either the wet versus dry hand press or the hand exposure monitoring methods. There is reason to believe that wet and dry hands differ (at least some of the time). There are no activity pattern data on the frequency or duration of wet or otherwise "sticky" versus dry hand events. In Part B Chapter 7 of the background document, there is no discussion of hand washes (e.g., rinses, wipes, etc.) nor of the efficiency of washes in 7.2.5.3. Reference and expansion of material in the Introduction Section (7.2.5) is needed. In addition, guidance on use of information on the effect of skin conditions (e.g., sebum content) on transfer rates must also be developed.

The guidance document should detail exposure evaluation methods and indicate how they relate to absorbed dose. Without an indication of absorbed dose exposure, evaluations have limited usefulness in risk assessment or risk management. The Panel will provide the Office of Pesticide Programs (OPP) and the OPP Docket with a list of references to be included in the document. These references should be reviewed and included in the document since they would provide basic knowledge that applicants would need to design and interpret useful studies.

The Agency must address the issues raised by the SAP report and incorporate those changes into the proposed 875 Part B guidelines prior to imposition of the non-dietary ingestion data requirement. Comments submitted by the Exposure Task Forces describe additional detailed examples of these issues raised by the SAP.

Most importantly, the guidelines should address the issues of data quality and criteria used for evaluation. Whether these data reported are adequate will depend on methods used, age of children, and the exposure setting. As an example, duration of contacts of young children with surfaces typically range from two to four seconds, so direct observations of multiple children or parental recall of behaviors will be inadequate to quantify these behaviors.

Finally, the background document should also address the following issues:

- a) evaluation of the efficiency of chemical residue transfer;
- b) timing of exposures;

- c) hand-to-mouth and object mouthing data that exist in the published literature but are not cited in the guidelines;
- d) repetitive contact and replenishment of hands after contact with surfaces; and
- e) repetitive contact and unloading of hands after contact with surfaces.

Dislodgeable foliar residue dissipation and turf transferable residue (Guideline 875.2100)

The proposed rule would change this requirement from “conditionally required” to “required”. However, in current assessments, the Agency often applies default factors to estimate Dislodgeable Foliar Residues (DFR) and Transferable Turf Residues (TTR). This approach is sensible because research has shown such estimates to be very conservative, if not upper-bound, and application of such defaults in lieu of empirical data can save significant resources if an assessment passes at such levels of DFR/TTR, because field study results are extremely unlikely to exceed default estimates. CLA encourages the Agency to maintain the current default policy, which promotes sensible allocation of resources, and to incorporate the policy in conditions for requiring this study. Thus, CR would continue to be the appropriate category.

Soil residue dissipation (Guideline 875.2200)

This proposal states that a soil residue dissipation study would be required for all occupational use sites and some residential ones, but later implies that the data are only needed to address risks from contact with “treated soil”. There is a tremendous difference between the two approaches that should be clarified. For some uses, most of the applied pesticide ends up in the soil. But for the vast majority of agricultural and residential use scenarios, there is currently no reason to believe that contact with treated soil is more than a negligible contributor to exposure. CLA recommends that this requirement be applied only for situations where soil is the main target of application, or exposure is of concern due to special circumstances, such as the persistence of the active ingredient (with specific parameters noted) or significant soil contact for the activity or activities in question.

Dermal and inhalation exposure (Guidelines 875.2400 and 875.2500)

The Preamble (p. 12280f) states that “EPA’s current post-application exposure data base is not comprehensive, especially regarding exposure to pesticides in nonagricultural settings.” CLA believes this statement is a mischaracterization. Both the Agricultural Reentry Task Force (ARTF) and the Outdoor Residential Exposure Task Force (ORETF) have supplied comprehensive post-application exposure databases in their respective areas and, as Agency scientists have stated, are at or very near completion of the scope of their work. These exposure databases include comprehensive data on typical foliage and turf exposure, but also include several more unique areas into which post-application requirements have been expanded, such as greenhouses, nurseries, golf courses, sod farms, residential gardens and ornamentals etc.

The Preamble also notes (p. 12302b), “The Agency has imposed two major DCI’s [sic] for dermal and inhalation exposure data for agricultural chemicals ... and for those applied to lawns...” However, no mention is made that these DCIs have been fulfilled primarily by ARTF and ORETF. CLA believes that some specifics are warranted regarding (1) the nature of the DCIs, (2) acknowledgement of the industry task forces’ role in their comprehensive fulfillment, and (3) the comprehensive nature of the ARTF and ORETF databases.

Use of Surrogate Data

The Preamble (Unit XIII.C.4, p. 12302c,d) notes that ARTF and ORETF are reliable sources for “some surrogate post-application exposure data,” but also states that “At this time, EPA generally is not allowing the use of surrogate data for any of the post-application residue data...”, i.e., DFR and TTR. This may be contradictory and slightly misleading for three reasons:

1. As noted above, the Agency has commonly applied default DFR/TTR estimates in its assessments, and such a practice warrants mention here. This effectively functions as surrogate information since the upper-bound values that are applied have been derived from a large number of studies.
2. Typically, within DFR and TTR research, only representative formulations are selected for field studies, using representative equipment, within a representative geographical area. Furthermore, DFR work is performed only on one or two representative crops, although some post-application-exposure activity clusters (as described in the ARTF database) include activities performed in numerous crops.
3. Although less common, two distinct active ingredients may have chemical and formulation properties so similar that one active ingredient can very reasonably stand as a surrogate for the other.

CLA believes the above technical points are very important qualifiers to the idea that surrogate data are not used for post-application residue, and warrant mention within this area.

Subpart N—Environmental Fate

General Comments:

In general EPA is codifying de facto requirements. A new Guideline numbering system (835.XXXX) replaces the existing series 161-166. Presumably there is a 1:1 correspondence between the old numbering system and the new one, except for some guidelines that were eliminated or transferred to other subparts (e.g. 165-3; accumulation in irrigated crops). Therefore the new guidelines and numbers should be posted on the EPA website. In addition, a distinction should be made between the OPP series 835 guidelines and the OPPTS series 835 guidelines.

Included in the environmental fate section are the two accumulation studies for fish (Guideline 850.1730) and non-target organisms (Guideline 850.1950) that would more appropriately be included in Subpart E, Terrestrial and Aquatic Nontarget Organisms. The rationale is similar to moving the rotational crop requirements (Guidelines 860.1850 and 860.1900) to Subpart O, Residue Chemistry.

The data requirements table and test notes do not mention degradates as test substances, though they have been required sometimes by EPA. The test notes should indicate this possibility and specify the potential triggers.

EPA should truly harmonize certain of its guidelines with the corresponding OECD guidelines in the areas of test system and test duration, so that duplicate studies are not required for other regulatory authorities.

Comments on Specific Guidelines

Hydrolysis (Guideline 835.2120; 161-1)

The expanded conditional requirement to include indoor food and nonfood and residential indoor uses appears logical.

Photodegradation in Water (Guideline 835.2240; 161-2)

Test note 2 appears to imply that the structural identities of the hydrolysis products are not needed to provide the UV information. If the hydrolysis mixture can be used to measure the UV, the proposed change would be more useful. If standards are required to generate the UV spectra, then the usefulness of this change is limited to older products with available standards or to products with hydrolytic stability.

Photodegradation on Soil (Guideline 835.2410; 161-3)

The change from “conditionally required” (CR) to “required” (R) for terrestrial use and forestry uses and the expansion to terrestrial nonfood uses merely codifies what is currently being done.

Photodegradation in Air (Guideline 835.2370; 161-4)

Expansion of CR to include all terrestrial, greenhouse, forestry, and residential outdoor use patterns should have little impact, although consultation with the Agency is recommended before tests are conducted. An information on trigger conditions should be included in test note 4.

Aerobic Soil Metabolism (Guideline 835.4100; 162-1)

Expanding the requirement to include aquatic uses on sites that are intermittently dry might require this study or a complementary DT₅₀ study on additional soil types, as the standard sandy loam soils might not be typical for aquatic uses.

Anaerobic Soil Metabolism (Guideline 835.4400; 162-3)

PMRA requires both the Anaerobic Soil and Anaerobic Aquatic studies, per PMRA Directive DIR2003-03 (the purported NAFTA "harmonized guidelines"). The studies evaluate two different aspects of degradation, and they aren't duplicative – the anaerobic soil study with aerobic pre-incubation investigates the degradation of the aerobic degradates under anaerobic conditions, compared with the purely anaerobic conditions of the anaerobic aquatic study.

However, the current EPA recommendation, as expressed in the Reregistration Rejection Rate Analysis (EPA 738R93010; 1993, <http://www.epa.gov/cgi-bin/claritgw?op-Display&document=clserv:OPPTS:0505.&rank=4&template=epa>), is that the registrant follow the guidelines for the anaerobic aquatic study for an anaerobic soil study. The guideline for the anaerobic soil metabolism study, Subdivision N of October 1982, states that "Data from an anaerobic soil metabolism study need not be submitted if data from the anaerobic aquatic metabolism study described in 162-3 of this subdivision have been submitted." This information should be included in a test note for the anaerobic soil guideline.

An open question is whether the combination of reinsertion of the anaerobic soil guideline and the expansion to terrestrial uses for the anaerobic aquatic metabolism study could require that two studies be performed, one with soil and water to satisfy 162-2 (835.4200) and one with sediment and water to satisfy 162-3 (835.4400). That interpretation would have a significant impact, doubling the time of the anaerobic system requirement. The inclusion of the above-mentioned note could clarify that one anaerobic study (presumably the anaerobic aquatic study, since current guidelines preclude substituting the anaerobic soil study) is sufficient, recognizing that the metabolites produced under anaerobic conditions would not vary significantly from sediment to soil.

Aerobic Aquatic Metabolism (Guideline 835.4300; 162-4)

Expanding the requirement to include all terrestrial and forestry uses codifies current practice.

Anaerobic Aquatic Metabolism (Guideline 835.4400; 162-3)

The issues mentioned for the anaerobic soil metabolism should be clarified and harmonized (with PMRA and perhaps OECD) to define which study or studies will satisfy the requirement to understand the behavior of the test substance in an anaerobic environment.

Leaching and Adsorption/Desorption (Guideline 835.1230; 163-1)

Although there were no changes to this requirement, the agency has shown a preference for the batch equilibrium method, since the Freundlich constants (used in several risk calculation programs) can be obtained directly. The guideline should be revised to reflect this preference.

Terrestrial Field Dissipation (Guideline 835.6100; 164-1)

The requirement for independent laboratory validation for analytical methods codifies what many in the industry are already undertaking. It is somewhat surprising that storage stability was not defined as a separate study, as it was for Subdivision O.

Including sites such as cranberry bogs and rice paddies could expand the number of sites needed for a typical dissipation study and involve soil types that could cause analytical challenges. The aquatic crop uses identified are often not on aquatic sites, but on drained arable agricultural lands with irrigation or water management controls to maintain water levels above the soil surface during part of the growing season. Regionally, rice fields can be rotated into corn, cotton, or soybean fields, for example. EPA must clarify if aquatic crop uses such as rice and cranberries would require a terrestrial field dissipation study (evaluating residues in soil) during the dry-land phase, in addition to an aquatic field dissipation study (evaluating residues in water and soil) during the flooded phase, both under actual use conditions. The Preamble indicates that "... the frequency of requesting this study will be quite low" due to the limited applicability of the change. The statement is misleading, however, if both Terrestrial Field Dissipation (TFD) and Aquatic Field Dissipation (AFD) studies are required for the aquatic crops, on top of TFD requirements for terrestrial crops. These "aquatic" agricultural lands need to be clearly distinguished from aquatic sites that cannot be used for upland agricultural purposes (ponds, lakes, marshes, streams), where in most years water is present throughout the year.

Greater impact could come with the merging of this guideline with 164-5, long-term field dissipation. The Preamble states: "The field dissipation study would be extended in duration for pesticides that are persistent so that the decline curves for the parent chemical and important degradates can be fully characterized." (p. 12303f) Since the samples are not necessarily analyzed at the current 18-month limit, the data for determining if a study should continue are not available, leaving the study open-ended. The TFD Workgroup decided on the following wording for the corresponding NAFTA guidelines, which would be appropriate for a 'test note' in the proposed rule: "The duration of the terrestrial field dissipation study, which is generally up to two years, should be sufficient to determine the DT₇₅ of the parent compound as well as the pattern of formation and decline of major transformation products in the soil. (NAFTA Guidance Document for Conducting Terrestrial Field Dissipation Studies. April 20, 2005. p. 17. See http://www.epa.gov/oppefed1/ecorisk_ders/efed_final_draft_tfd_guidance.pdf and 70 FR 34758, 6/15/2005.)

The last sentence on p. 12303 of the Preamble ("Since the expanded.... will be quite low.") appears to be out of place, as the identical wording appears later in the aquatic field dissipation section on p. 12304. Its occurrence in either location is confusing.

Aquatic Field Dissipation (Guideline 835.6200; 164-2)

To be consistent with the previous section the Agency should state that aquatic food crops, like rice and cranberry uses, which are managed to have a dry-land period for production, now must be conducted under the TFD guideline. The Agency is expanding the aquatic field dissipation (AFD) study use pattern to include terrestrial food, feed and nonfood uses. It is not clear in the PR Notice why the Agency is conditionally requiring this use expansion for the AFD guideline. However, one might assume from the “conditions” (high persistence, high mobility, etc.) that an aquatic site field study would be useful for determining the non-target fate of terrestrial pesticide use. If the test chemical has any one of the aforementioned properties, would aquatic field dissipation studies be triggered? Triggers for the conditions, such as DT₅₀ for persistence and K_{oc} for mobility, should be defined in the test notes. If this is the reason for the use expansion, then field procedures in the guideline should be revised significantly to indicate the appropriate amount and method of pesticide application to the test system. The exposure to an aquatic system, if it is not the intended target site (e.g. runoff from a treated field), will be quite different than if it is the intended site of application (e.g. aquatic herbicide, rice paddy, etc.); thus registrants will need guidance on appropriate application rates. The requirement would also add the need for an official analytical method for residues in water with a defined LOQ, since water methods developed for ecotox analyses typically have a fairly high LOQ.

The AFD guideline (OPPTS 835.6200, EPA Subdivision N 164-2) is often cited as the basis for environmental fate field studies of non-crop aquatic-use products, for example, aquatic herbicides. The 1982 guideline is inadequate in describing the goals and procedures for this kind of study. Recent aquatic fate field studies in the literature use appropriate protocols, and the Agency should consider revising this guideline in the near future with the help of experts in this area. The cost of such a study would be significant with potentially little relevant information to be gained. A tiered approach with modeling could be used to determine the need for this study.

Forestry Dissipation (Guideline 835.6300; 164.3)

One would expect a field dissipation study to be required for a forestry use. The CR status for this study in the forestry use pattern should be explained through listing in test notes the conditions where such a study would and would not be required, such as extrapolation of data from other field dissipation studies.

Combinations and Tank Mixes (Guideline 835.6400; 164-4)

Test note 9 provides no useful information on when such data are needed, and should be made more relevant. In the vast majority of cases, the presence of a minute level of one substance in soil does not affect the rate of degradation of another substance. This premise is the basis of registration for many package and tank mixtures. If there is scientific evidence for specific substances that refute this premise, then it is reasonable for EPA to require mixture studies.

General Comment on Field Dissipation Studies and Combinations and Tank Mixes

In general, all outdoor uses of a pesticide should be supported by at least one field dissipation study for whichever use pattern is most appropriate. One study may be sufficient to extrapolate for other use patterns. For some formulations, such as fumigants or insect traps, the requirement can be waived. With such data available, there should rarely be a requirement for a specific

study on a combination product or tank mix, since the presence of one active ingredient in soil does not significantly alter the rate or route of dissipation of another one.

Accumulation Studies (Guidelines 850.1730; 850.1950; 165-4; 165-5)

Test note 10 is very helpful, and should be a model for other test notes to define trigger conditions. It should apply to accumulation studies aquatic non-target organisms also, replacing test note 11, which says the same thing more vaguely. In addition, the test material for Aquatic Nontarget Organism Accumulation (850.1950) should be PAIRA which would be more useful in most cases. Furthermore, the relationship between these two studies and guideline 860.1400 (residue in fish, irrigated crops, and potable water) should be clarified. We suggest that Hydrolysis (835.2120), Aquatic Metabolism (835.4300/835.4400), and the cited accumulation studies can serve as either triggers for, or perhaps meet, the 860.1400 data requirements. It would be more appropriate to include these studies in Subpart E, since the new guideline numbers suggest that this was already considered.

Groundwater Monitoring (Guideline 835.7100; 166-1/166-2)

The requirement appears to cover both prospective and retrospective groundwater monitoring and is probably consistent with current practice, although the existing guidelines are not well defined, and consultation with Agency scientists is always a prerequisite. The conditions for this requirement in test note 10 should focus on the results of the field dissipation studies rather than laboratory studies.

The proposed guideline should include guidance on how to interpret the study results. For example, while the study results are useful in estimating the extreme upper-bound pesticide concentrations in drinking water, the guideline must explain that use of a residue value from a single high water sample is not appropriate for conducting long-term safety evaluations. Therefore, the guideline will need good instructions on how to synthesize the groundwater results, which often contain censored data due to method sensitivity, and present them in useable format (with time-weighted averages, for example).

The Preamble states (p. 12304d) that PGW studies "... are also often the best tool with which to estimate pesticide concentrations in drinking water drawn from shallow private wells." This does not reflect reality, as people do not generally drink shallow water from directly under treated fields. Modeling should replace the PGW study as a more appropriate intermediate Tier in determining the upper bound estimates of potential groundwater contamination. The preamble also states that PGW studies will continue to be used to 'improve' models. Enough PGW data has already been generated to improve existing models, and develop effective new screening models (e.g., SCIGROW). If a potential groundwater impact is still in question, a retrospective monitoring program (preferably tap water or drinking water wells) in targeted high use areas is more useful in determining human exposure.

Subpart O—Residue Chemistry

In general CLA agrees that the proposed changes to Subpart O are not substantive and that they codify practices that have become common when fulfilling requirements for registration of a new use or new pesticide over the last two decades.

Definition of a tolerance (§180.1200)

The proposed rule should reference or reiterate a more useful and complete definition of “tolerance.” The definition expressed here tells what range of administrative tolerance actions and applications are covered by the data requirements, but does not say what a tolerance actually is. Furthermore, the definition implies that all of the data requirements and conditions apply to applications for a tolerance exemption, which cannot be the case. If it can be demonstrated on the basis of toxicity and exposure data that an exemption from a tolerance is in order for a particular pesticide chemical, whether it is an active ingredient or an inert ingredient, then plant metabolism, animal metabolism, and magnitude of the residue data would not be required.

Requiring residue data for nonfood uses

§158.1210(b)(2) mentions that “Food uses in general require a more extensive database to characterize, whereas nonfood uses which are of shorter duration, may require fewer studies.” It is unclear whether this means that (1) all nonfood uses are of shorter duration than food uses and thus require fewer studies, or (2) those nonfood uses of shorter duration would require fewer studies than nonfood uses of longer duration. The meaning of “duration” in this context and how it applies to study requirements is a mystery.

Meat/milk/poultry/eggs (Guideline 860.1480)

The Preamble states (p. 12307c) that “... the Agency proposes to change the test substance for the meat/milk/poultry/egg study (guideline 860.1480)... to a single plant metabolite instead of metabolites in plural.”

Conducting separate feeding studies for individual metabolites to determine the magnitude of the residue is an unnecessary and inappropriate burden. The number, types, and relative quantities of metabolites of concern in meat, milk, poultry and eggs should be determined from the livestock metabolism study (Guideline 860.1300), in comparison with the toxicology studies conducted under Subpart F. If different metabolites or degradates of toxicological concern occur in plants (i.e., livestock feed), whether due to actual metabolism in the plants or to uptake of unique soil metabolites or degradates (as experience has shown can occur), than result directly from livestock metabolism, the subsequent fate of those different compounds should be investigated in the context of the livestock metabolism study, not in the livestock feeding studies. Combined results of the metabolism studies in both livestock and plants should determine the mix of TGAI and metabolites that should be used in the livestock feeding studies. The magnitude of the “total toxic residue” can be appropriately determined in the livestock feeding study (guideline 860.1480) by either quantitation of the individual significant residues via LC/MS/MS (or other suitably sensitive instrumentation), or by quantitation of the total residue by a common chemophore method. Tolerances are not determined separately for individual metabolites, and therefore the total residue is the appropriate data for magnitude of the residue

studies, whether by summing individual metabolites in the same samples or by a common analyte formed by hydrolysis or other degradative means.

Anticipated Residues

EPA should clarify the relationship of requirements for anticipated residues, discussed at p. 12307f, to the provisions of FFDCA §408(b)(2)(E) on “Data and information regarding anticipated and actual residue levels.”

With respect to “anticipated residues,” The Preamble “... proposes to indicate in the test note that alternative data, such as market basket surveys, may be required.” (P. 12307f; see also test note 22, p. 12353b.)

In the past, Market Basket Studies have been conducted on a voluntary basis by registrants or task forces, usually in the process of reregistering a pesticide or group of pesticides. The size, labor requirements, and cost of a statistically sound market basket survey can be prohibitive. Because of the undue burden it could place on a single registrant, market basket studies should only be conducted on a voluntary basis, as has been the practice to date. The need for such a study, its size, and the commodities monitored should be evaluated on a case-by-case basis between the registrant and the Agency.

The Agency also proposes “... to address the need for residue data on acutely toxic pesticides in single servings of raw agricultural commodities ...” since most residue data are taken from composited samples. Again, this type of study should remain on a voluntary basis, as negotiated with the Agency. The extra cost for collection of single serving samples can be unnecessarily burdensome. Numerous single-serving studies done by USDA’s Pesticide Data Program, registrant task forces (Carbamate Market Basket Survey, OP Market Basket Survey), and individual registrants have consistently shown that residue distributions do not differ significantly between composite samples and single servings of a given commodity, even in side-by-side comparisons. Substantial scientific evidence in hand does not support the need for single serving residue data in most circumstances.

Residue Chemistry. (§158.1210(a)(2))

The generalization that “All residue data requirements ... are required for an experimental use permit” (§158.1210(a)(2), p. 12350d) ignores current practice as well as practicality. It could substantially increase the data burden for EUPs without sufficient thought and analysis, and render most EUPs impractical. The residue chemistry data are required to establish a tolerance for dietary residues. A crop-destruct EUP can be granted to allow some expanded field testing under conditions where there will be no dietary exposure for humans or livestock. Some EUPs have no relationship to food- or feed-crop uses. This statement should be deleted or modified to apply to “all uses for which tolerances are required.”

Furthermore, the Field Rotational Crop study (Guideline 860.1900) was not an EUP requirement when it was categorized under Environmental Fate, and should not become an EUP requirement, merely because it has been moved to Subpart O.

Residue data for indoor uses

The changes made to classification of use patterns lead to some confusion with respect to test note 1 (p. 12351b): “Required if indoor use could result in pesticide residues in or on food or feed.” This test note is transferred from the current Part 158, where the residue chemistry data requirements table lists only an “indoor” use pattern (no further modification), while the proposed rule lists only an “indoor food” use pattern in the table in Subpart O. One would assume that “indoor food” uses would have the potential for exposure to food and thus require many if not most of the listed residue chemistry studies, and establishment of tolerances. Occasionally an “indoor nonfood” use might have potential for food exposure, and thus require some of the residue studies, but rarely establishment of tolerances. Further clarification of how indoor uses are divided among “food” and “nonfood” categories is necessary to determine the appropriateness of test note 1 and its application to the various residue chemistry requirements. This situation further emphasizes the need to keep the listing of individual uses and use pattern categories as part of the regulation.

§158.1210(b)(2) discusses a variety of nonfood use patterns that may require residue data on a case-by-case basis of exposure to food or feed may occur. The agency has not deemed it necessary to include these use pattern categories in the table in 158.1210(d). Thus it should not be necessary to imply in test note 1 that some of the specific residue data requirements might apply to indoor uses other than indoor food uses.

Rotational Crops (Guidelines 860.1850 & 860.1900)

The general area of residue testing in rotated crops and the resultant tolerance requirements remains one of the most perplexing pesticide regulatory topics. The starting point for 860.1850 studies with three crops and three plant-back intervals is clear, but how the various different potential outcomes, in light of field dissipation results (835.8100), are interpreted to trigger subsequent testing (860.1900), define tolerance requirements (860.1560), and impact directions for use (860.1200) is confusing at best, and arbitrary from the perspective of many registrants. In that regard, test notes 7 and 23 have not been modified from their use in the environmental fate table in the current §158.290. They merely restate subjective fundamentals, and do not help to identify actionable triggers. EPA must rethink and restate the data requirements and logical relationships among the above cited guideline numbers in a more reasoned and quantitative manner.

Home garden uses

Test note 3 indicates data are required on both nature and magnitude of residue for uses that involve food crops in home gardens. However, proposed food tolerances (860.1550) are NR for residential outdoor uses. This dichotomy is present in the current Part 158 also, and reflects the general inconsistency relating to pesticides labeled and marketed for home garden or orchard use. Plant metabolism studies should be required for home garden use only if it represents the sole food crop use for the active ingredient (a highly unlikely situation), in which case a proposed tolerance (Guideline 860.1550) would be required. Field residue data should be required for home garden only if (1) it represent the sole use for a particular crop (proposed tolerance, Guideline 860.1550 would be required) and no other crop residue data can reasonably be translated to that crop, or (2) the conditions of use are substantially and demonstrably different from the commercial crop use such that residues are likely to be higher (both highly

unlikely situations). The Agency should take this opportunity to rethink and restate a reasoned approach to all data requirements related to dietary exposure arising from pesticide use in home garden food production, up to and including roadside sale of local produce.

Residue Analytical Methods (Guideline 860.1340)

Often the Agency has sought radiovalidation of the residue analytical method, because it is a straightforward and scientifically valid demonstration that the method is appropriate for quantifying the residue. However, if the metabolism study shows acceptable material balance (>90%) and the extraction procedure is identical to that for the residue method, radiovalidation is not necessary. It would be appropriate to address radiovalidation under both the Nature of the Residue and the Analytical Method entries, since there are alternate solutions to this requirement.

Processed food or feed (Guideline 860.1520)

Test note 15 states that both nature and magnitude of residue in processed food or feed are required if residues concentrate on processing. In practice, radiolabeled processing studies to define changes in the nature of the residue are seldom conducted, whereas processing studies to determine the concentration factor(s) for residues in processed foods are routine. The Agency has not had reason to require subsequent magnitude-of-the-residue data for processed foods involving random or structured sampling to confirm the accuracy or validity of a calculated concentration factor. Furthermore, test note 15 is not listed for either of the metabolism studies. This test note should eliminate the mention of metabolism studies and should indicate that the intent of the study is to determine if and to what quantitative extent concentration of residues occurs in processed foods.

Storage Stability Data (Guideline 860.1380)

The proposed rule requires a storage stability study to validate the Magnitude of the Residue studies. The proposed rule should explicitly allow the flexibility of including the required storage stability data within the magnitude of residue study for certain studies, e.g., processed fractions and livestock feeding studies. This approach has worked well in the past, saving time and cost.

Subpart R - Spray Drift

Even though no changes are proposed for spray drift data requirements at this time, the current §158.440 cannot simply be transferred intact to the revised Part 158. The current §158.440 refers to other numbered sections that either disappear or are substantially changed in the proposed revisions. Furthermore, the use patterns in that data requirements table may not match the newly expanded use categories.

It seems that the new Subpart R should begin with §158.1400 rather than §158.1410, to be consistent with the numbering scheme for other subparts.

Subpart U – Applicator Exposure

The Preamble states (Unit XVI.B.2, p12308f) that “...if the agency knows that a particular product or class of products is frequently used in a manner that isn’t directed on the label, the Agency can still require data.” This statement could be interpreted to mean that the agency intends to require data to support off-label uses. No registrant intends any of its products be used in any manner other than those specifically approved on the label. Each product label specifically and clearly states that use of the product inconsistent with label instructions is a violation of federal law. Any off-label uses or misuse of a product must be dealt with by appropriate enforcement action, rather than requiring additional data to “support” the misuse. An official EPA policy of this nature undermines the legality of an EPA-approved label.

Dermal Exposure Studies (Guidelines 875.1100 and 875.1200)

The proposed rule codifies data requirements for both outdoor and indoor dermal exposure studies. Because few changes were made in updating these guidelines from the previous guidelines (230 and 231), the methodology described in the newer guidelines is not current and is inconsistent with the methodology now being used in studies. For example:

- a) The guidelines call for dermal exposure pads and envelopes. Current methodology uses whole body dosimeters (WBD) for both inner and outer dosimeters. While the use of pads should not be excluded, WBDs give a more accurate measure of exposure and should be the methodology of choice. The use of WBD is currently not even mentioned as a form of residue measurement.
- b) The current guidelines recommend 95% ethanol for hand rinses. However, most if not all Agency-approved protocols call for the use of anionic detergent solution (e.g., Aerosol[®] OT solution) for hand washes. Most protocols also use a bowl to wash the hands in rather than a zip type bag attached at the wrist. Both methods should be supported.
- c) The guidelines recommend patches for the head, alternatively this exposure can be estimated from the shoulder, chest, and back exposures. Most studies now use neck and face wipes to measure exposure. Another weakness of the patches is that exposure to some areas must be estimated from exposure to the patches in other areas of the body. WBD methodology allows exposure to be measured in areas such as upper and lower arms, front and rear torso, upper and lower legs and chest without extrapolation from other areas.
- d) No references are cited.

Inhalation exposure studies (Guidelines 875.1300 and 875.1400)

The proposed rule codifies data requirements for both outdoor and indoor inhalation exposure studies. Because few changes were made in updating these guidelines from the previous guidelines (230 and 232), the methodology described in the guidelines is not current with that now being used in studies. For example:

- a) There is very little discussion on the use of pumps and sampling media for use with pumps. Much discussion is given to the use and preparation of the modified respirators, a methodology seldom to never used in this country.
- b) Twenty-nine L/min is cited as a light work inhalation rate. This actually corresponds to the moderate to heavy inhalation rate from the Exposure Factors Handbook. The guidelines also cite 2 L/min as the minimum airflow acceptable for studies. Most pumps are calibrated for less than this value (1-2 L/min).
- c) There is no discussion of field fortification for OSHA Versatile Samples (OVS tubes) or similar sampling devices, the handling of the OVS field samples, or the availability of a myriad of OVS samplers.
- d) The most recent reference for this guideline is 1982 with at least one reference dating back to 1956.

Biological monitoring (Guidelines 875.1500)

CLA supports the inclusion of biological monitoring as a conditional data requirement. The discussion of biological monitoring (Guideline 875.2600) and human pharmacokinetic data under Subpart K in these comments is also pertinent to this requirement (Guideline 875.1500) in Subpart U.

Data reporting and calculations information (Guideline 875.1600)

The proposed rule requires registrants to submit data reporting and calculation information whenever handler exposure data are submitted.

General Comments:

- a) The current guidelines do not mention GLP report requirements
- b) The current guidelines do not mention PR 86-5 report-writing guidelines.
- c) The current guidelines mention submitting data in a format compatible with the Pesticide Handlers Exposure Database (PHED), though this database is being replaced through efforts of the Agricultural Handlers Exposure Task Force. The Agency needs to address how new surrogate data will be incorporated into existing databases.

Product use information (Guideline 875.1700)

EPA is proposing to require product use information (guideline 875.1700) as part of the revisions to Subdivision U. The product use information will provide the Agency with information about how the pesticide is actually used, including all relevant application parameters such as rate, timing, equipment, etc. This would enable the Agency to conduct more accurate and realistic risk assessments, leading to appropriate mitigation measures if needed.

This guideline has not been finalized in the OPPTS Harmonized Test Guidelines for Occupational and Residential Exposure. See the opening paragraph in our comments under Subpart K.

Peer Review of Residential Exposure Data Requirements

The Preamble mentions (Unit XVIII.B.4, p. 12311e) that the post-application exposure guidelines and standard operating procedures (SOPs) were presented to the SAP in 1998 and 1999. But those two presentations dealt with very different material. The 1999 SAP presentation was specific to the HED Residential SOPs and did not address the concerns (which have yet to be resolved) raised by the SAP in 1998 regarding indoor residue dissipation and non-dietary ingestion in the Series 875 Part B guidelines. Therefore, the statement in the Preamble that “In 1999, the SAP approved and commended the Agency for making significant strides toward developing scenario-based residential and non-occupational exposure assessments that are sufficiently conservative as to not underestimate exposures” is not relevant to the exposure assessment guidelines. The Preamble should clarify that the SAP has not approved or commended the Series 875 Part B data guidelines.