



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

AUG 15 2008

OFFICE OF
CHIEF FINANCIAL OFFICER

The Honorable Dianne Feinstein
Chairman
Subcommittee on Interior, Environment
and Related Agencies
Committee on Appropriations
United States Senate
Washington, D.C. 20510

Dear Chairman Feinstein:

Thank you for your commitment to the U.S. Environmental Protection Agency's (EPA) work to develop and implement the Endocrine Disruptor Screening Program (EDSP). Pursuant to the report language in the FY 2008 Interior and Environment appropriations bill, I am notifying the Committee that EPA expects to begin issuing test orders for Tier 1 screening of the initial list of chemicals under the EDSP after the August 2008 requested start date.

Let me update you on accomplishments made this year and our expectations for the next several months. As you may already know, EPA currently is implementing the EDSP in three major parts. Along with the development of a battery of validated assays to screen chemicals for their potential to interact with the endocrine system, identifying candidate chemicals for testing and describing procedures for issuing test orders are fundamental to EPA's approach to implementing the EDSP.

Significant progress was made as EPA sought public comment on both its "Draft List of Initial Pesticide Active Ingredients and Pesticide Inerts to be Considered for Screening under the Federal Food, Drug, and Cosmetic Act" and "Draft Policies and Procedures for Initial Screening." The Agency also proposed a Tier 1 battery to be used for screening the initial list of chemicals. The proposed Tier 1 battery was reviewed by the FIFRA Scientific Advisory Panel (SAP) on March 25-27, 2008. In addition to the validated assays used for screening and testing chemicals, EPA concurrently is pursuing an ambitious research program to develop predictive tools to help prioritize chemicals for future screening and testing.

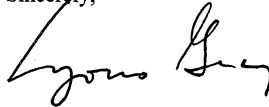
While EPA has made significant progress, the Agency recently concluded that additional time is needed to complete necessary steps before it is able to begin issuing orders. EPA is addressing comments in the June 2008 report from the FIFRA SAP on the proposed Tier 1 battery. The Agency also is responding to a Request for Correction regarding one of the assay validations, filed in July 2008 under EPA's Information Quality Guidelines by the Center for

Regulatory Effectiveness. In addition, EPA is preparing a response to a petition to delay the EDSP orders received in July 2008 from Crop Life America, the trade association representing pesticide manufacturers. Also, the comment periods for both the "Draft List of Initial Pesticide Active Ingredients and Pesticide Inerts to be Considered for Screening under the Federal Food, Drug, and Cosmetic Act" and "Draft Policies and Procedures for Initial Screening" were extended several times. Public comments raised a number of complex regulatory, policy, and scientific issues that the Agency currently is addressing that affect final decisions on the design of the screening program.

Please be assured that the Agency is working as quickly as possible to resolve all outstanding issues so that the screening program can continue to move ahead in a manner that is scientifically sound and meets all applicable legal requirements. EPA is currently in the process of completing its final preparation of the interagency review packages for the related documents, and intends to expedite the remaining procedural and administrative steps for completing those documents. Once the related Information Collection Request is approved under the Paperwork Reduction Act (44 U.S.C. 3501 et seq.), EPA will begin to issue the orders in early 2009.

If you have further questions, please contact James B. Gulliford, Assistant Administrator for the Office of Prevention, Pesticides and Toxic Substances at (202) 564-2902, or your staff may call Ed Walsh in the Office of the Chief Financial Officer at (202) 564-4594.

Sincerely,

A handwritten signature in black ink, appearing to read "Lyons Gray". The signature is written in a cursive, flowing style.

Lyons Gray
Chief Financial Officer

Pesticide Licensing and Endocrine Disruptor Screening Activities Report to Congress

Report Language: Given that the Committee has restored funding for the Endocrine Disruptor Program, it expects the Agency to accelerate its schedule for completing validation of screening and testing assays. To that end, the Committee directs the Agency to report to Congress within six months of enactment of this Act, and annually thereafter, on:

- (a) The number of pesticides that EPA has registered or reregistered, and the number of pesticides for which EPA has made either a reregistration eligibility decision, issued a tolerance, or conducted a registration review, since August 3, 1999;
- (b) The number of such pesticides for which EPA has conducted or required testing for endocrine disrupting effects;
- (c) The number of such pesticides for which EPA has considered and made a determination regarding endocrine disrupting effects;
- (d) The number and identity of endocrine disruptor screening and testing assays EPA has validated;
- (e) The number and identity of endocrine disruptor screening and testing assays EPA has not validated;
- (f) The reasons each assay has not been validated.

The Committee encourages the Agency to expedite its validation of Tier 2 screening and directs the Agency to include in this report a schedule for completing validations for Tier 2 screening testing assays.

EPA Report

(a) The number of pesticides that EPA has registered or re-registered, and the number of pesticides for which EPA has made either a re-registration eligibility decision, issued a tolerance, or conducted a registration review, since August 3, 1999;

Agency Response: In preparing its response to this question, EPA considered the following types of regulatory actions it took during the period from August 3, 1999 through September 30, 2007 (the end of fiscal year 2007):

- Issuance of Reregistration Eligibility Decision documents (REDs);
- Issuance of initial registrations of pesticide products containing an active ingredient that did not appear in any previously registered pesticide; and
- Issuance of new or amended registrations for a pesticide product for a use which required EPA either to establish or modify a tolerance or tolerance exemption.

The Agency then identified each unique active ingredient and inert ingredient associated with one or more of these regulatory actions. The total number of active and inert ingredients associated with these actions was 958. This total includes 372 REDs, 222 Registrations and 364 tolerance actions. The Registration Review program was initiated in February 2007 and 25 cases were opened in FY 2007. Risk assessments are in progress.

(b) The number of such pesticides for which EPA has conducted or required testing for endocrine disrupting effects;

Agency Response: The Agency routinely requires a pesticide applicant to submit data from a range of toxicity studies (see 40 CFR, Part 158). The specific data requirements will vary depending on the active ingredients and their proposed use patterns. A number of these studies provide information on endocrine-related effects, including: the rat 2-generation reproduction study, mammalian subchronic bioassays (in rats and dogs), mammalian chronic bioassays (in rats and dogs), cancer bioassays (in rats and mice), mammalian prenatal developmental studies (usually in rats and rabbits), the developmental neurotoxicity study (in rats), fish reproduction studies (usually in fathead minnow and rainbow trout), avian reproduction studies (usually in bobwhite quail and mallard duck), and an estuarine/marine invertebrate life cycle study (usually in mysid shrimp).

Of the 953 pesticides counted in the answer to question (a), the Agency received data from testing conducted by pesticide registrants for an estimated 500 pesticides that provided information on endocrine-related effects through one or more of the above referenced assays. Of the estimated 500 pesticides, 48 have been tested with the Endocrine Disruptor Screening Program (EDSP) mammalian Tier 2 assay (the rat 2-generation reproduction study based on the 1998 test guidelines). Another 33 have been tested with a full life cycle or partial life cycle fish reproduction assay, 242 have been tested with an avian reproduction assay, and 63 with a mysid reproduction study. In most instances a single pesticide has been tested in more than one of these assays.

(c) The number of such pesticides for which EPA has considered and made a determination regarding endocrine disrupting effects;

Agency Response: EPA has evaluated all of the 953 pesticides counted in the answer to question (a), and has found that all meet required statutory safety standards. Under the FFDCA EPA has found that there is a reasonable certainty that no harm will result from exposure via the diet and other non-occupational pathways. Moreover, in associated registration decisions under FIFRA, EPA has concluded that the use of the pesticides will not pose unreasonable risks to the environment. In evaluating potential risks of a pesticide, EPA's regulatory decisions ensure protection of human health, wildlife and aquatic life from the most sensitive adverse effects observed in the information base provided through mammalian and wildlife studies such as those listed in (b). Of the 953 pesticides counted in the answer to question (a), endocrine-related effects were the most

sensitive effects observed within the information base for 67 pesticides and, therefore, used for regulatory purposes.

(d) The number and identity of endocrine disruptor screening and testing assays EPA has validated;

Agency Response: Ten Tier 1 assays for the endocrine disruptor screening program have undergone the validation process, including peer review. They are as follows:

1. Uterotrophic
2. Hershberger
3. Female Pubertal
4. Adult Male
5. Male Pubertal
6. Androgen Receptor Binding
7. Aromatase
8. Amphibian Metamorphosis; and
9. Fish Screen
10. Steroidogenesis

The Tier 1 screening battery proposed by EPA for the March 2008 review by the Scientific Advisory Panel (SAP) contained ten of the assays listed above (all except the adult male) plus the estrogen receptor binding assay, which is still undergoing validation.

In addition, EPA included in the proposed battery an estrogen receptor reporter gene assay that was validated by Japan and is being adopted as an Organisation for Economic Co-Operation and Development (OECD) test method.

(e) The number and identity of endocrine disruptor screening and testing assays that EPA has not validated;

Agency Response: EPA is in the process of validating one assay for Tier 1:

- 1) estrogen receptor binding assay.

(f) The reasons each assay has not been validated.

Agency Response:

The estrogen receptor binding assay has not been validated because of recent technical difficulties experienced by the labs. These technical difficulties can cause labs to overstate the measurement of various values by a significant magnitude. For example, a lab may report 750 percent binding of the receptor (the theoretical maximum is 100

percent), necessitating a repeat of the experiment. The cause of the anomalous measurements is unknown but these discrepancies have occurred in more than one lab.

Also, there is occasional unexplained drift or change in the behavior of the reference chemical between the beginning and end of an experiment. The problem is intermittent, not systematic, making its cause difficult to pinpoint. The problem is significant because it prevents establishment of good performance criteria for the assay. Performance criteria are required in order to demonstrate that a laboratory is performing the assay correctly. Lastly, the variability of the assay upon replication contributes to validation delay.

Another example is a separate effort through the OECD. In validating the human recombinant ER (hrER) assay recently, it was determined that radioligand from the supplier degraded quickly and led to low radioactivity counts, which would contribute to variability. This possibility is being investigated for the ER binding assay using rat uterine cytosol as well. There are many other potential sources of variability, and identifying those responsible for the disappointing results seen so far in the interlaboratory validation study has required significant additional work.

Controlling variability is important in maximizing the sensitivity of the assay. EDSP continues to believe that the assay can be validated for identifying chemicals that have the potential to bind with the estrogen receptor, but notes that the assay has been far more difficult to validate than expected.

The Committee encourages the Agency to expedite its validation of Tier 2 screening and directs the Agency to include in this report a schedule for completing validations for Tier 2 screening and testing assays.

Agency Response:

For Tier 2, EPA is in the process of validating the following four assays:

1. Avian 2-generation
2. Amphibian Growth/Reproduction
3. Fish 2-generation
4. Mysid 2-generation

If the need for Tier 2 testing is triggered for any of the chemicals initially identified for screening under Tier 1, testing can then be initiated. EPA accepts one of the Tier 2 assays for the endocrine disruptor program, the Mammalian 2-generation assay, as valid. Validation for the remaining four assays (Avian 2-generation, Amphibian Growth/Reproduction, Fish 2-generation, and Mysid 2-generation) is scheduled for 2010 at which time the assays will be ready for use.

Validation of these assays required more time because they are longer term assays that take a year or more to complete. Validation must proceed stepwise with protocol optimization and standardization, followed by a demonstration that it can be transferred

to another lab before the interlaboratory validation study can be run. Thus, these tests must be run sequentially, not in parallel.