Chapter 7

Implementation

Do Not Cite, Quote, or Distribute

Table of Contents

I. Introduction

This chapter is intended to provide information on the statutory requirements, regulatory and administrative processes, and the timeline that flows from these requirements and processes that will govern EPA's implementation of EDSTAC's recommendations. Since EDSTAC did not make recommendations regarding administrative implementation questions (e.g., testing orders, consent agreements, rules, etc.) the discussion of these types of issues in this Chapter represent a preliminary indication of EPA's plans rather than EDSTAC's recommendations.

The fundamental requirements that must be met are set forth in the FQPA:

I. Using validated assays, EPA must propose a screening program by August 1998;
II. EPA must implement the proposed screening program by August 1999; and
III. EPA must report the results of the screening program to Congress by August 2000.

A.

B. A timeline that describes the key processes and their relationship to each other is provided in Figure 7.1. They include:

C.

IV. EDSTAC and SAB/SAP Peer Review Processes;
V. High Throughput Pre-Screening (HTPS) Feasibility Demonstration and Utilization;
VI. Final Development, Utilization, and Maintenance of the Endocrine Disruptor Priority Setting Database (EDPSD) and Completion of the Priority Setting Process;
VII. Standardization, Validation, and Utilization of the Tier 1 Screening Battery and Newly Developed Tier 2 Tests; and
VIII. EPA Regulatory and Administrative Processes (e.g., FQPA Orders, TSCA Consent Agreements and/or Rulemaking) Related to the Endocrine Disruptor Screening and Testing Program (EDSTP).

A.

II. High Throughput Pre-Screening Feasibility Demonstration and Utilization

The HTPS has been validated for its use to screen new pharmaceutical products; however, it has not been used to screen pesticides, industrial chemicals, environmental contaminants, and mixtures. The EDSTAC has recommended that 15,000 chemicals and a small number of mixtures should be subjected to a selected set of assays using high throughput technologies. The range of chemical structures within this list is much more diverse than has been the experience with this technology to date.

Therefore, as a first step in implementing the EDSTP, EPA has already initiated an effort to demonstrate the feasibility of the HTPS for the diverse set of chemical substances and mixtures that are recommended for inclusion in the HTPS step of the process. EPA intends to complete the feasibility demonstration project under a contract with a commercial laboratory that specializes in running these assays.

In addition, as per the recommendation of the EDSTAC, EPA plans to make use of the EDSTAC's HTPS Task Group to continue to provide advice to the Agency on a variety of issues related to the HTPS feasibility demonstration project. Such issues include, but may not be limited to criteria for selecting chemical substances and mixtures that should be the focus of the feasibility demonstration.

After completion of the feasibility demonstration efforts, and assuming it confirms the feasibility of HTPS, EPA plans to conduct the HTPS on as many as 15,000 pesticides, industrial chemicals, and a limited number of mixtures. EPA is soliciting industry's assistance to supply samples of chemicals for the HTPS. A cooperative program is beneficial because conducting the HTPS under a regulatory program would greatly delay its implementation. As described below, the data from the HTPS will be incorporated into the EDPSD and will be used by EPA in conjunction with other exposure- and effects-related information to set priorities for T1S. The

HTPS data should be available in mid-1999, thus meeting the minimum statutory requirement to screen for estrogenic effects over one year before the deadline.

III. Final Development, Utilization, and Maintenance of the Endocrine Disruptor Priority Setting Database (EDPSD) and Completion of the Priority Setting Process

As described in Chapter Four, the EDSTAC began to develop the EDPSD as a tool to assist in priority setting. The intent is to assemble existing data sources and databases into an interrelational database to assist in understanding the "real-world" implications of alternative approaches to priority setting. Although a prototype was partially built during the EDSTAC process, there was insufficient time to include all important data sources and databases, or to perform adequate quality control on those that were included. The EDSTAC recommends the Agency should complete the development and test the utility of the EDPSD as a tool for managing the data needed for making final Agency decisions on priorities for T1S. EPA believes that the further development of EDPSD could occur simultaneously with the feasibility demonstration and utilization of the HTPS. Thus, HTPS data could be included in the EDPSD prior to final decisions on priorities for the first phase of T1S.

The EDSTAC has also recommended that the Agency convene a multi-stakeholder process, similar in makeup to the EDSTAC, but smaller in size and much more focused and limited in its objective. Specifically, the multi-stakeholder process would be used to solicit reaction to the progress made by the Agency on the EDPSD prior to its final completion. ~~After the incorporation of the HTPS data, those involved in the process would use the EDPSD as a means to provide input to the Agency on its final decisions on priorities for the first phase of T1S.~~ Following the completion of the notice and comment~~multi-stakeholder~~ process, EPA would then make and publicly announce its final decisions in the form of a Federal Register Notice that would include list of chemicals that would be subjected to T1S during Phase I of the EDSTP. In addition to the multi-stakeholder process, EPA should seek public comment on the database tool before using it which should allow for comments on the tool itself, comments on EPA's

interpretation of the HTPS data, and submission of additional chemical specific data to be incorporated in the tool. After receiving comments on the tool, EPA should also propose for comment its priorities for T1S.

IV. Research Program to Address Low Dose Testing Issues

As noted in Chapter Five, serious issues have been raised as to the adequacy of classical approaches to regulatory toxicity testing that employ exaggerated dosing regimens (up to maximally tolerated dosages) in order to identify a hazard. The EDSTAC is incorporating some interim measures to address those CSMs that will bypass T1S and proceed to Tier 2 Testing (T2T) in Phase I of the EDSTP. In addition, the EDSTAC is recommending additional research to resolve the controversies about the nature of the dose-response curve for endocrine active substances, particularly with regard to the low dose region. EDSTAC has recommended that EPA develop a collaborative program involving government, industry, and appropriate individuals in academia to design the study protocols, be kept abreast of the conduct of the studies, evaluate results, and develop overall conclusions and recommendations. EPA and other EDSTAC members are beginning to define the list of research topics for the group to address.

V. Standardization, Validation, and Utilization of the Tier 1 Screening Battery and Newly Developed Tier 2 Tests

As noted in Chapter Five, none of the assays being recommended by EDSTAC for T1S are validated, and only a few of the proposed tests in T2T are validated. In Section VII. F. of Chapter Five, EDSTAC recommends that a multi-stakeholder process involving government, industry, and academics be utilized in standardizing and validating the T1S and T2T batteries.

EPA has stated its intention to initiate a standardization and validation program for all recommended screening ~~of the~~ assays and tests ~~recommended in T1S~~ to provide flexibility in designing the~~a~~ screening and testing program~~battery~~. EPA is requesting industry's cooperation in carrying out this validation. The validation program will be limited to no more than 20 chemical substances and ~~probably~~ involve three or more ~~no more than two~~ sets of laboratories (ideally taking place in industry, government, and contract laboratories). ~~Thus, each assay will be run in two laboratories~~ The standardization and validation process should be done according to the principles outlined by national and international alternative methods validation groups, specifically ICCVAM and ECVAM.

It is estimated that even this limited standardization and validation process will take two years to complete. Assuming this process begins in August 1998, it will not be completed until August 2000. Standardization and validation of the individual assays and battery is the rate-limiting step in initiating the actual screening and testing that will occur in the EDSTP. Thus, taking into account the necessary regulatory and administrative procedures, as explained in the next section, what might be considered the first phase of T1S and T2T would commence toward the end of the year 2000.

[NOTE TO THE READER: The following text grew out of discussions at the March plenary; however, EPA staff and the facilitation team recommend that EDSTAC members review this and the other proposed multi-stakeholder efforts with an eye towards consolidation and coordination.]

EDSTAC recommends that EPA convene a multi-stakeholder committee to provide technical expertise and feedback on implementation of the Endocrine Disruptor Screening and Testing Program (EDSTP). The technical committee will consider such issues as the following:

- adequacy of range finding in the T1S screening battery;
- implementation of new procedures for other hormone systems and in other animals;
- plans for prioritization of chemical substances and mixtures;
- selection of mixtures beyond initial EDSTAC recommendations;
- new research areas;
- interpretation of initial and preliminary results to verify and confirm that the assays used in screening and testing continue to provide the expected output;
- whether the processes and procedures are working as planned and expected by EDSTAC; and

testing and screening and ultra-low doses and the research program to examine this issue for inclusion in the EDSTP.

EPA should insure that adequate resources are available for the full participation of multiple stakeholders in such a technical committee. EPA and other federal agencies may need to provide technical assistance grants to community groups or other NGO's for their representation on this committee.

VI. The EPA Regulatory and Administrative Process

EPA plans to base its proposal for an EDSTP on the recommendations made by EDSTAC. EPA plans to initiate its formal proposal for the EDSTP through a notice in the Federal Register in August 1998. After receiving comments on its formal proposal, and at the conclusion of the HTPS, EPA will utilize a multi-stakeholder process to help the Agency determine the priority of chemical substances and mixtures for T1S. The Agency will propose this list in the Federal Register in the fall of 1999.

As per the EDSTAC's recommendation contained in Chapter Four, priorities for the first phase of T2T will follow the FQPA tolerance reassessment schedule for food-use pesticides, or be set on a case-by-case basis for the limited number of chemicals in addition to food-use pesticides that meet the criteria for bypassing T1S.

The results of the standardization and validation effort for the T1S battery, along with guidelines for the screening assays that flow from this effort, will be published in the Federal Register in late 2000. The standardization and validation of Tier 2 Tests will be undertaken approximately in parallel with that of the screening battery. However, the EDSTAC and EPA have given less attention to the nature and timing of the standardization and validation effort that will be needed for the Tier 2 Tests. By virtue of the longer nature of the Tier 2 Tests, the test validation program will probably take longer than the screening validation program.

In early 2001, EPA could issue testing orders to the first group of pesticides and other chemical substances that are subject to the authority provided to EPA under the FQPA and SDWA. EPA will also solicit voluntary industry efforts to initiate T1S for those chemicals that are not subject

to FQPA/SDWA authority. This effort will include, but may not be limited to, the development of enforceable consent agreements (ECAs) for screening the highest priority TSCA chemicals. In parallel to these activities, EPA will initiate a TSCA test rule to require phased screening of chemicals not covered by the FQPA/SDWA. This TSCA test rule will be proposed in 2001 and finalized in 2002. The length of time between phases and number of phases will depend on the number of chemicals proposed for screening. EPA may decide to issue more than one rule for the EDSTP. T2T for chemicals that are part of the first phase of T1S would begin after review of screening data indicated that testing was warranted.