Chapter Four

Priority Setting

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[NOTE TO READER: The PSWG is in the process of collecting and inserting references for this chapter. This draft provides an indication of where those references will be inserted in the text.]

I. Introduction

A. Charge to the PSWG

This chapter of the EDSTAC Report addresses the need to set priorities for endocrine disruptor screening and testing. It was developed by the Priority Setting Work Group (PSWG) and reviewed, refined, and endorsed by the EDSTAC. The PSWG consisted of 19 individuals representing a wide diversity of perspectives and backgrounds including various sectors of industry; a variety of state and federal government agencies; national environmental, worker, and public health-oriented organizations; and local citizen and environmental justice groups. A complete list of work group members is included in Appendix C. References and sources for this chapter can be found in Appendix F.

The charge given to the PSWG was to:

1. *Specify types of information that should be gathered and analyzed to sort and prioritize chemical substances and mixtures for screening and testing;*

A.

1. *Develop criteria for evaluating the quality, adequacy, and reliability of the information that will be used in sorting and prioritizing chemical substances and mixtures for screening and testing;*

B.

1. *Develop criteria for sorting chemical substances and mixtures into four possible next steps, including: a) hold screening and testing; b) prioritize for Tier 1 Screening; c) go to Tier 2 Testing; or d) go to hazard assessment;*

C.

1. *Develop criteria for setting priorities for Tier 1 Screening. These criteria will address the relative order of priority in which chemical substances that are sorted into this category will actually proceed to Tier 1 Screening;*

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D.

1. *Suggest how information used for priority setting should be combined with screening and testing results to generate a "weight-of-evidence" determination for proceeding from screening to testing or from testing to hazard assessment.*

B. The Need for Priority Setting

Priority setting for endocrine disruptor screening and testing is not a trivial exercise. Industrial chemicals, pesticides, commercial products, and environmental contaminants have been subjected to various screening and testing regimes for decades (Swanson and Socha, 1997). However, the existing regulatory screening and testing schemes do not specifically address endocrine disrupting mechanisms. The chemicals in commerce and the environment exhibit a range of dramatically different physical/chemical and toxicological properties, as well as varied production and use patterns. Only some chemicals are likely to cause endocrine disruption, and only some of these chemicals will be produced or used in such a fashion that humans or other living organisms will be exposed to them. Because screening and testing can be such a resource-intensive process for both the public and private sectors, priorities must be set carefully to ensure that the chemicals of greatest concern are given priority over chemicals of little or no concern.

The challenge is daunting. As described in Chapter Two, the universe of chemicals that need to be considered for endocrine disruptor screening and testing is quite large. In addition to environmentally degraded chemicals, there are currently more than 75,500 chemicals listed in the TSCA Inventory (James Darr, U.S. EPA, personal communication). There are approximately 600 pesticide active ingredients and 1,800 inert pesticide ingredients that are used to formulate over 20,000 pesticide products (John Housenger, U.S. EPA, personal communication). The EDSTAC also recommends ~~There are~~ approximately 8,000 chemicals regulated by the Food and Drug Administration (FDA)~~, which the EDSTAC is recommending be a part of the federal government's endocrine disruptor screening and testing program. This~~ including~~es~~ 5,000 ingredients in cosmetics and 3,000 food additives, including those Generally Regarded As Safe (GRAS) under the Food, Drug and Cosmetic Act (Bern Schwetz, FDA, personal communication) should be evaluated for possible inclusion in the endocrine disruptor screening and testing program. The EDSTAC recognizes, however, that if these chemicals are determined to be a priority for screening and testing, it will require a cooperative effort among the responsible agencies. Finally, the EDSTAC also recommends that nutritional supplements be considered for endocrine disruptor screening and testing.

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However, since these chemicals are not currently regulated by the FDA, or by any other agency, the EDSTAC was unable to estimate the total numbers of chemicals within this category. Thus, the universe of chemicals that should be considered for endocrine disruptor screening and testing is approximately 86,000.

In responding to the challenge, the PSWG grappled with a number of practical considerations:

What scientific criteria should be used in establishing priorities?
What information is available with respect to these criteria and how readily can the information be analyzed?
What are the major gaps in information needed for setting priorities and how can these gaps be filled?
How should the priority setting system be designed to maximize "transparency" (i.e., public understanding of the rationale underlying the established priorities)?
Should priorities be governed by existing statutory authorities?
How might priorities be set, without regard to EPA's statutory authority, to encourage voluntary private sector testing and to ensure compounds of concern are addressed?

The EDSTAC's efforts to develop a coherent, scientifically sound framework for setting screening and testing priorities have required EDSTAC members to carefully review the tools EPA has available for gathering information about new and existing chemicals. The Committee examined the tools provided to EPA by Congress which guide the Agency's data-gathering efforts, and reviewed the Agency's management of the data available to it. The Committee also reached beyond EPA in its quest for pertinent information sources to guide priority setting. Data on chemical hazards in the environment are also gathered by the Occupational Safety and Health Administration, the U.S. Department of Agriculture, the Food and Drug Administration, the U.S. Department of the Interior, and other federal and state agencies.

Despite the multitude of data-gathering authorities and databases on chemicals, information on exposure to and the health and environmental effects of chemicals are ~~grossly~~ incomplete, ~~uneven, and especially~~ inadequate with respect to endocrine disrupting effects. For example, much more information is available on the effects of pesticides regulated under FIFRA than is available on the effects of industrial chemicals addressed under TSCA~~, even though the production volumes of chemicals addressed by TSCA dwarf the production volumes for pesticides, and the number of chemicals addressed by TSCA is more than 35 times the number of~~

~~chemicals addressed by FIFRA~~. The EDSTAC's priority setting scheme attempts to address these information disparities.

The priority scheme recommended in this chapter is noteworthy in several other respects, reflecting an integrated, scientifically driven concern for chemical exposures and effects that transcends the barriers to integrated data gathering and response that exist under current federal law. It is important to note that the following discussion of EDSTAC's recommended priority setting scheme do not reflect any interpretation by EDSTAC of EPA's authority to implement these recommendations.

First, even though the immediate impetus for endocrine screening and testing lies in provisions contained in the FQPA and the amendments to the SDWA, as described further below, the EDSTAC has not limited its priority setting scheme to chemicals addressed only under the endocrine disruptor screening and testing provisions contained in those two statutes.

Second, as described in the Conceptual Framework contained in Chapter Three, the EDSTAC has not limited its attention to the estrogen mimics that are the stated primary focus of the FQPA and SDWA, but is recommending that the initial program also include androgen- and thyroid-related hormones. The Committee also recommends review of the initial program to evaluate whether the inclusion of additional hormonal systems is warranted in the future.

Third, even though the FQPA and the SDWA focus on human health, the EDSTAC decided early in its deliberations that the endocrine disruptor screening and testing program should address environmental impacts as well.

Fourth, the EDSTAC recommends that the endocrine disruptor screening and testing program should address chemical mixtures in addition to single chemicals.

Fifth, the priority setting scheme, by promoting the use of robotic screening technologies (referred to as High Throughput Pre-Screening, or HTPS), is designed both to generate new information about chemicals and to help validate chemical modeling techniques that are used to judge hazards in the absence of "real world" data.

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Sixth, the Committee deliberately included so-called "phytoestrogens," substances that naturally occur in the environment, in its priority setting scheme. These can be used to validate screening and testing protocols.

As further outlined below, the EDSTAC's priority setting scheme is driven by an over arching concern with exposures to and effects from chemicals, while the Committee acknowledges that, for obvious reasons, EPA's screening and testing actions will be both heavily driven and constrained by its statutory authority.

II. Overview of the Sorting and Priority Setting Recommendations

A. Initial Sorting Step

As described in Chapter Two, and graphically depicted in Figure 4.1, the EDSTAC Conceptual Framework consists of three major components: 1) the sorting and priority setting component; 2) the Tier 1 Screening (T1S) component; and 3) the Tier 2 Testing (T2T) component. Within the sorting and priority setting component, the EDSTAC has made a distinction between the tasks of "sorting" and of "priority setting." The term "sorting" is used to refer to the initial effort to sort the universe of chemicals that will be considered for endocrine disruptor screening and testing into four distinct categories. Coming out of the initial sorting box, the four possibilities include:

polymers which will be placed into a "hold" status (with some exceptions) pending a review of their monomers, oligomers, and other components;
chemicals for which insufficient data exist to proceed to either T2T or hazard assessment and will, therefore, need to be prioritized for T1S;
chemicals for which sufficient data exist to go to T2T; and
chemicals for which sufficient data exist to go to hazard assessment.

The term "priority setting" refers primarily to the need to set priorities for the chemicals that fall into the second category after the initial sorting stage. (It will also be necessary to set priorities

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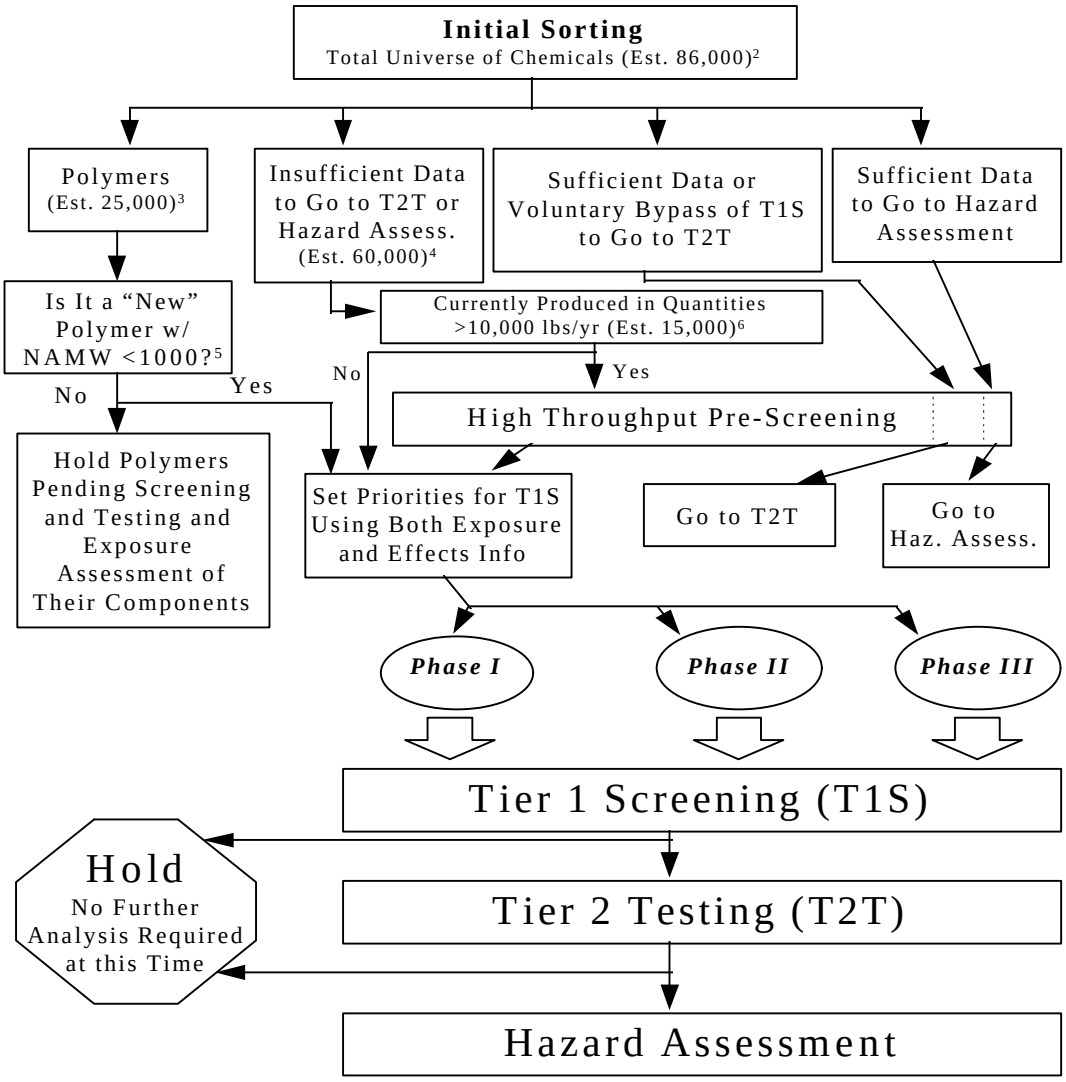
Figure 4.1

Detailed Depiction of EDSTAC Conceptual Framework[1]



[1] This flow chart represents a more detailed description of the sorting and priority setting components, and how they relate to the Tier 1 Screening (T1S), Tier 2 Testing (T2T) and Hazard Assessment components.
[2] Please refer to Chapter 4, Section I. B.
[3] Please refer to Chapter 4, Section VI. A. 2.
[4] Please refer to Chapter 4, Section II. K. Essentially, this number results from subtracting 25,000 polymers from the total universe of 86,000 chemicals.
[5] Please refer to Chapter 4, Section VI. A. 1.
[6] Please refer to Chapter 4, Section V. F.

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for chemicals that fall into the third category, although the EDSTAC's recommendations for chemicals in this category are necessarily much less complex than for those that fall into the second category.)

The remainder of this section provides a brief overview of each of the four categories flowing from the initial sorting step, as well as some of the other key features of the priority setting system recommended by the EDSTAC. The sections that follow build upon this overview section.

B. Polymers

In an effort to grapple with the very large number of chemicals the PSWG had identified as candidates for endocrine disruptor screening and testing, the group spent considerable time addressing the question of which, if any, chemicals should be placed in the "hold box" as part of the initial sorting step. It thought that if a class, or classes, of chemicals has a very low probability of being endocrine disruptors for the hormonal systems addressed by the screening and testing program, it could perhaps be set aside so as to avoid "clogging up" the system.

The group identified one type of chemical that warranted further consideration – polymers. It was initially thought that polymers, because of their molecular size, would not pose a threat to the endocrine systems of humans and other biota. However, upon further research, the group learned that there are instances where polymers could be absorbed, particularly in neonates – an obvious cause for concern. As explained in more detail in Section VI. of this chapter, the EDSTAC recommends that:

i? All monomer and oligomer components of polymers should be prioritized for and subjected to endocrine disruptor screening and testing.

i? All "new" polymers (i.e., those produced after the Initial TSCA Inventory, which was published in 1979) with a number average molecular weight (NAMW) less than 1,000 daltons should also be prioritized for and subjected to endocrine disruptor screening and testing.

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a?

i? All previously manufactured polymers and all "new" polymers with a NAMW greater than 1,000 daltons should be set aside pending the outcome of the screening and testing of their monomer and oligomer components.

i? If the component is determined to have endocrine disrupting properties, the component sh~~would proceed to hazard assessment.

a?

As with any chemical shown to have endocrine disrupting properties, an exposure ~~risk~~ assessment will be performed. ~~Although discussion of the specifics of risk assessment is outside of the purview of the EDSTAC, it is important to note that, in addition to the hazard assessment referred to in (4) above, an exposure assessment for the component will be conducted. A~~ It is at this stage, all potential exposure routes for a component would be determined, including the potential for the component to be available from the polymer.

As indicated in Figure 4.1, if this approach is utilized it will place approximately 25,000 (James Darr, U.S. EPA, personal communication) polymers of the approximately 86,000 chemicals being considered for endocrine disruptor screening and testing into a hold box pending a review of their monomers and oligomers. The rationale for these recommendations, as well as the recommendations themselves, are elaborated upon in Section VI of this chapter.

C. Chemicals with Sufficient Data to Go to T2T

As noted in Chapter Three, the EDSTAC recognizes that pesticides regulated under FIFRA, especially food-use pesticides, will generally have substantially greater toxicological and chemical use information available than the vast majority of industrial chemicals regulated under TSCA (Anthony Maciorowski, U.S. EPA, personal communication). In addition, it was recognized that, in a limited number of cases, industrial chemicals may have significant amounts of toxicological data available. Thus, the EDSTAC recommends that chemicals for which two-generation toxicological studies have been completed, but where the previously conducted tests did not include the recommended endocrine disruptor endpoints for T2T should be permitted to bypass T1S and go directly to T2T. However, it is recommended that these chemicals should still be subjected to HTPS for reasons that are outlined below. In addition, as noted in Chapter Three, chemicals that meet this criterion for bypassing T1S will

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be the most likely candidates for the alternative means of completing T2T, described in Chapter Five, Section VII.

Chemicals that meet this sorting criterion would be separated into two categories: 1) food-use pesticides; and 2) all other chemicals. Food-use pesticides constitute 469 of the approximately 600 pesticide active ingredients (John Housenger, U.S. EPA, personal communication). As described in more detail in Section XI. G., the recommended approach for setting priorities for food-use pesticides is basically to follow the schedule for pesticide re-registration and tolerance reassessments for these chemicals, as per the schedule and requirements of the FQPA. The priorities for conducting T2T on the non-food-use pesticide chemicals that meet this criterion ~~other than food-use pesticides~~, which the EDSTAC believes is likely to be a very small number, would be made on a case-specific basis.

D. Chemicals with Sufficient Data to Proceed to Hazard Assessment

The EDSTAC recommends that chemicals for which there is sufficient data to conduct a hazard assessment should be permitted to bypass both T1S and T2T and proceed directly to the hazard assessment step of the process. This option should be available for chemicals that have sufficient data to make either a definitive positive or negative determination that the chemical either does or does not have endocrine disrupting properties for the estrogen, androgen, and thyroid hormonal systems addressed by the program.

This step in the process will require a case-specific review and determination that the same type and quality of information exists for the chemical as would be necessary to move from T2T to hazard assessment. The "petitioner" of such a chemical (or EPA in the case of an "orphan" chemical) would need to show that the screens and tests conducted yielded data that are the "functional equivalent" of data that would have been produced from T1S and T2T. Such functional equivalency will certainly include sufficient dose-response relationship clarification before proceeding to the hazard assessment phase.

The EDSTAC believes that only a small number of chemicals will meet this criterion; however, it did not attempt to identify these chemicals. Rather, the Committee has appropriately deferred this decision to EPA as part of the implementation of the endocrine disruptor screening and testing program. As noted above, such a decision will need to be made on a case-specific basis. When EPA formally proposes its approach to implementing

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the Endocrine Disruptor Screening and Testing Program (EDSTP), the Agency should publish more detailed decision-making criteria, data and reporting requirements, and procedures petitioners will need to follow to provide the degree of clarity necessary to implement this recommendation.

E. Chemicals with Insufficient Data to Go to T2T or Hazard Assessment

A very large number of chemicals will remain after the initial sorting step has separated out polymers (with some exceptions), food-use pesticides and other chemicals that have functionally equivalent data to bypass T1S, and the small number of chemicals that will be ready for the hazard assessment step. The EDSTAC estimates the number of chemicals that will fall into this category to be approximately 60,000. The EDSTAC has developed a set of recommendations to guide the T1S priority setting process for these chemicals.

F. Priority Setting Information Categories and Criteria

When the PSWG began its deliberations, the group sought to address the following questions:

1? What information is relevant to the task of priority setting?
2? Is this information readily available?
3? If so, how easily can the information be accessed?
4? What is the quality, variability, and reliability of this information? and
5? Can the information be used as the basis for criteria to determine priorities for endocrine disruptor screening and testing?

In grappling with these questions, the PSWG established three main categories for organizing information and criteria related to priority setting: exposure-related, effects-related, and statutory criteria. The exposure and effects categories and information are consistent with those in Swanson and Socha (1997). Under each of these main headings, the group identified a number of subheadings:

1. <u>Exposure-Related Information and Criteria</u>

a)
Biological sampling data
i? Human

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ii? Other biota

b)
Environmental, occupational, consumer product, and food-related data
i.
Air
ii.
Water (including surface water, groundwater, and drinking water)
iii.
Soil/sediments
iv.
Consumer products
v.
Food
c)
Environmental releases
d)
Production volume
e)
Fate and transport data and models

2. *<u>Effects-Related Information and Criteria</u>*

a)
Toxicological laboratory studies and databases
b)
Epidemiological and field studies and databases
c) Predictive biological activity or effects models
d)
Results of high throughput pre-screening

3. *<u>Statutory Criteria</u>*

a)
Pesticides, as per FQPA
b) Chemicals found in sources of drinking water affecting significant populations, as per SDWA

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c)
Chemicals that may have a cumulative effect with pesticides, as per FQPA

For the exposure and effects criteria, the PSWG identified a significant number of data sources, evaluated the quality and strengths and limitations of these data sources, and determined how to best utilize these data sources to accomplish the task of priority setting. The results of this effort are set forth in Section III for the exposure-related criteria, and in Section IV for the effects-related criteria. Appendix G includes a series of detailed matrices containing a list and preliminary evaluation of data sources organized under the effects and exposure subheadings.

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G. Role of the Statutory Criteria

The PSWG of the EDSTAC discussed the proper role of the statutory criteria listed above in relation to the other criteria. It is the understanding of the EDSTAC that the screening and testing requirement for pesticides contained in the FQPA is mandatory. However, the EDSTAC understands the other two statutory criteria requiring the screening and testing of: 1) chemicals found in sources of drinking water affecting significant populations under the SDWA, and 2) chemicals that may have a cumulative effect with pesticides under the FQPA, to be discretionary.

~~*Notwithstanding the discretionary nature of the latter two criteria, EPA does have the authority to issue orders to compel endocrine disruptor screening and testing for chemicals that meet any one of these three criteria through a Section 4 TSCA test rule, through a consent agreement, or through other means. It is also the understanding of the EDSTAC that EPA's testing authorities under TSCA do not permit the Agency to issue orders to compel screening and testing (as is possible under FQPA/FIFRA). However, EPA can require endocrine disruptor screening and testing under TSCA, under certain circumstances, through a Section 4 test rule. Alternatively, the Agency can negotiate consent agreements for testing under TSCA; this is currently the more prevalent approach.*~~

While recognizing the importance of the statutory criteria in relation to EPA's implementation authorities, the Committee has developed its priority setting recommendations based on public health and environmental concerns rather than on narrow legal considerations. Thus, the
| *Committee recommends that the statutory criteria should not be used as a sole basis for establishing priorities for endocrine disruptor screening and testing. The Committee recognizes that this recommendation might result in a chemical substance or mixture being identified as a high priority for endocrine disruptor screening and testing for which EPA might not have*
| *authority to require ~~compel~~ such screening and testing under FQPA~~, at least in the short-term~~. Nevertheless, the Committee believes it is important to have priorities driven by scientific considerations and explicit value judgments, rather than by narrow legal considerations.*

| *The Committee is hopeful that when a chemical is identified as a high priority for T1S that falls*
| *outside of the scope of the FQPA, ~~and EPA does not have the authority to compel screening in the short-term (i.e., through an order issued under its FQPA/FIFRA authority),~~ the owner of the*
| *chemical would voluntarily conduct T1S and, if necessary, T2T. ~~This situation would arise primarily for TSCA-regulated chemicals. If such a voluntary effort were not undertaken, EPA~~*

~~could still rely on its testing authorities under TSCA.~~ The Committee acknowledges, however, that reliance on ~~such~~ authority other than FQPA may affect the timing of actually conducting T1S, notwithstanding the priority ranking of the chemical.

H. High Throughput Pre-Screening (HTPS) Step

One problem the PSWG identified early on in its deliberations is the lack of endocrine disruptor effects-related data on the vast majority of chemicals and their degradates. The PSWG considered recommending the use of published and available Quantitative Structure Activity Relationship (QSAR) models to obtain predictions for the endocrine disrupting potentials of untested compounds. However, a review of the available QSAR models revealed that they were of insufficient quality with respect to the diversity of chemicals that needed to be considered for endocrine disruptor screening and testing (references to be inserted). Therefore, it was the PSWG's determination that QSARs were currently incapable of providing accurate predictions for this highly diverse universe of chemicals. To rectify this problem, the work group recommended, and the plenary endorsed (subject to a demonstration of feasibility), incorporating into the EDSTAC Conceptual Framework the use of "high throughput pre-screening," or the use of automated processes (robots and specialized instrumentation) to aid in the screening of compounds (discussed in more detail in Section V. of this chapter).

The primary purpose of HTPS would be to address the fact that there is very little, if any, biological effects information for humans, and even more so for other species, on the vast majority of chemicals to be considered for endocrine disruption screening and testing. The assays that will be conducted during the HTPS step of the process are transcriptional activation assays for the three hormonal systems (estrogen, androgen, and thyroid-related), which are the initial focus of the endocrine disruptor screening and testing program. Had the EDSTAC not recommended that these assays be conducted as part of the HTPS step of the process, they would have been included in the T1S assay battery.

It is important to acknowledge, however, that the assays in the HTPS step will be far from comprehensive or definitive. They will certainly provide valuable information on the potential of a chemical to exert an endocrine disrupting effect, which is information that is missing for a large number of chemicals. However, the results of HTPS will not be sufficient by themselves to support the conclusion that a chemical is or is not an endocrine-mediated toxicant.

It is also important to note that the data resulting from HTPS will be combined with exposure-related information, and with any other effects-related information that is available for each chemical for the purpose of setting priorities for T1S. In other words, HTPS data will neither be used in isolation of other relevant data nor will it become the *de facto* determinant of priorities for T1S.

Although the use of robotic technology will greatly expand the "throughput" of chemicals over a given period of time for the selected assays, the EDSTAC does not recommend that all chemicals that fall into the category of those needing to be prioritized for T1S be subjected to HTPS. Rather, the EDSTAC recommends that the estimated 15,000 chemicals currently produced in an amount equal to or greater than 10,000 pounds per year be the set of chemicals subjected to HTPS. The EDSTAC makes this recommendation in order to help EPA avoid a task that might never be completed if a higher number of chemicals were to be recommended for HTPS. Also, the EDSTAC believes that 15,000 chemicals is not an insignificant number of chemicals, especially given the history of TSCA.

The EDSTAC further recommends that chemicals permitted to bypass T1S and go directly to T2T, as well as those permitted to bypass both T1S and T2T and go directly to hazard assessment due to functional equivalency of data, should also be subjected to HTPS. However, as described more fully in Section V. G. 2., the results of HTPS for these chemicals would not be used to set priorities for T1S. Rather, the results would be used to develop QSARs and to inform dosing considerations and the types of tests that would need to be conducted in T2T for those chemicals for which T2T will be conducted.

The EDSTAC recommends that existing QSAR models be rederived and supplemented with data from the HTPS assays, thereby expanding the predictive ability of these models. Existing QSARs are derived using data from cell-free receptor binding and cellular proliferation assays. These assays are part of Tier 1 Screening assays, as specified in Chapter Five, Section III. New QSARs using HTPS data and transcriptional activation potencies from whole cell assays will need to be developed. These new models will likely be expansions of existing QSARs if the same chemical compounds are included in both.

Thus, when it comes time to set priorities for the first phase of T1S, HTPS data (as well as improved QSARs) should be used along with other relevant exposure and effects data. Chemicals not subjected to HTPS (because they are produced in amounts less than 10,000 pounds per year), but which are selected for T1S during the first phase of the program, would still have to complete

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the transcriptional activation assays conducted during the HTPS step as part of the T1S battery of assays.

It is envisioned that the process of QSAR model expansion and improvement will continue in a cyclical feedback manner, thus providing the opportunity to validate the QSAR models using external data sets for screens and tests of compounds not subjected to HTPS. Eventually, endocrine disruption potentials obtained from validated QSAR models could be used as surrogates for HTPS data for compounds for which effects data are not available.

I. Inclusion of Mixtures and Naturally Occurring Non-Steroidal Estrogens and Recommendation for a Nominations Process

The EDSTAC recommends in subsequent sections of this chapter that EPA include a discrete number of mixtures (see Section VII) and naturally occurring non-steroidal estrogens (see Section VIII) in the endocrine disruptor screening and testing program. In addition, the EDSTAC recommends that a process, separate and distinct from the core priority setting process, be conducted to allow affected communities and members of the public to nominate chemicals for screening and, if necessary, testing (see Section IX).

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J. Introduction of the Endocrine Disruptor Priority Setting Database (EDPSD)

The PSWG struggled with how to use the information sources and criteria it identified to sort and prioritize chemicals for endocrine disruption screening and testing. At its October 1997 plenary meeting, the EDSTAC, in response to work group information and queries, directed the PSWG to consider developing a computer database to store electronic information related to criteria that could be used for sorting and prioritizing. The EDSTAC was careful to instruct the PSWG not to develop a list of what were then referred to as "high priority chemicals for Phase I screening," but rather to develop a tool to illustrate different scenarios that could show the implications of alternative choices for setting priorities.

During the October 1997 PSWG meeting, the PSWG asked two of its members to develop a relational database containing information sources associated with various criteria to facilitate the sorting and prioritizing processes, pursuant to Committee guidance. The members developed the database with a significant amount of assistance from an EPA contractor. This database is referred to as the Endocrine Disruptor Priority Setting Database (EDPSD). A preliminary version of the EDPSD was presented to the EDSTAC at its December 1997 plenary.

The EDSTAC was impressed with the speed at which the EDPSD could provide different scenarios, and gave unanimous support for continued development of the EDPSD. However, it became clear at the December 1997 plenary that there would not be sufficient time or resources available to fully complete the development and validation of the EDPSD within the time frame of the EDSTAC's deliberations. Following the December 1997 plenary, the PSWG was told that EPA would complete and validate the EDPSD. Section X. of this chapter provides a more detailed description of the EDPSD, including the data fields that were entered by the December 1997 plenary, the data fields the EDSTAC recommends that EPA enter, and a process for using the EDPSD.

K. Overview of the Recommended Approach to Priority Setting

In the concluding section of this chapter (Section XI), the EDSTAC presents its recommendations for how to set priorities: a) for chemicals that will need to be considered for T1S; and b) for chemicals that meet the criterion for bypassing T1S and going directly to T2T.

The recommended approach for setting priorities for the approximately 60,000 chemicals that will need to be considered for T1S builds upon the EDSTAC's recommendations to: screen mixtures

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and naturally occurring non-steroidal estrogens; establish a separate and distinct nominations process; separate out food-use pesticides and other chemicals that have sufficient data to bypass T1S; and utilize a database tool to help analyze information relevant to priority setting. The recommended approach is one that would have EPA, with continued advice and assistance from a multi-stakeholder group, use the EDPSD to help set priorities that flow from a simple and transparent application of the exposure- and effects-related information categories and criteria. The EDSTAC recommends that EPA apply the information categories and criteria outlined in Sections III. and IV. in a manner that would explicitly state the percentage of the total number of chemicals to be subjected to T1S in any one phase of the program to be drawn from the data sources for each criterion, or from the explicit combinations of criteria. This approach, which is referred to as a "compartment-based" approach to priority setting, is described in more detail in Section XI.

The recommended approach for setting priorities for chemicals that meet the criterion for bypassing T1S and going directly to T2T, in the case of food-use pesticides, is to use the schedule EPA has established for tolerance reassessments and pesticide re-registration under the FQPA. All other chemicals that meet this criterion would be addressed on a case-specific basis.

III.
Exposure-Related Information and Criteria

This section describes in more detail the types of exposure-related information and criteria that the EDSTAC recommends be used as the foundation for the priority setting process for T1S. Exposure-related information and criteria consist of four exposure information categories and one fate and transport information category.

The four exposure-related information categories are: a) biological sampling data for humans and other biota; b) environmental, occupational, consumer product data, and food-related data; c) data on environmental releases; and d) data on production volume. These four exposure-related information categories can be viewed as a hierarchy or spectrum in an exposure chain. Detecting a chemical in a biological sample means that exposure has actually occurred and has led to a body burden for that chemical. Detection of a chemical in an environmental medium, or knowledge that the chemical is in a consumer product or food where it is likely to lead to internalization, indicates that an organism is likely to be directly exposed to the chemical. Knowledge that a

chemical is released into the environment indicates that a chemical is likely, depending upon its chemical and/or physical properties, to be present in an environmental medium in which organisms live and, therefore, exposure is possible. If a chemical is being produced, it is possible that it could be released into the environment and, therefore, an exposure could occur; however, chemicals could be entirely consumed in making a product in a closed system and never released to the environment (e.g., site-limited intermediates).

A major limitation of the more direct measures of exposure is that they include only those chemicals for which there exist analytical techniques. The EDSTAC came to refer to this problem as "lamp post science." While production data, in contrast, exist for a large number of chemicals, the link between production data and exposure is tenuous.

The fate and transport information category includes chemical and/or physical properties that may be used to predict or estimate the medium or media where a chemical is likely to be found and whether or not a chemical is likely to remain in the environment over time. This information can be used in several ways. Since new chemicals will not have any data in the four exposure-related information categories, the fate and transport information, along with estimated production information, can be used to estimate concentrations in environmental media. Fate and transport information can also be combined with known production volumes or environmental release information to estimate concentrations in environmental media. The more direct the measure of exposure that is combined with fate and transport information, the more likely one would anticipate the estimates to be of actual conditions. Unlike the other exposure-related information categories which contain measurable empirical data, fate and transport information consists of estimations and predicted and/or calculated data.

The remainder of this section describes in more detail the nature of the information included in each exposure-related information category, the strengths and limitations of the type of information in each category, and a recommended set of guiding principles for how to use the information contained in each category to complete the task of setting priorities for endocrine disruptor screening and testing.

A. Biological Sampling Data

Biological sampling refers to the monitoring of information related to chemicals found in tissues or media from living or previously living organisms, thereby documenting actual human or animal exposure. The biological sampling information category includes data that falls into two

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subcategories: 1) human biomonitoring; and 2) monitoring of other biota. Human biomonitoring refers to monitoring of human tissues and media (e.g., blood, breast milk, adipose tissue, and urine) in discrete populations. Monitoring of other biota encompasses the sampling of a very wide range of species (invertebrates, fish, and wildlife) and sample matrices (e.g., carcass, liver, kidney, egg, feathers, etc.) for exposure to environmental contaminants.

Strengths

Human

1? Data are evidence of actual human exposure
2? Many data sets are representative of large populations; other data sets are representative of disproportionately exposed populations
3? Can be used to provide data to address mixtures
4? Generally good quality data; however, this must be determined on a case-specific basis
5? May be used to identify trends
6? For those substances monitored, can evaluate frequency and magnitude of exposure detections relative to each other to help prioritize
7? Addresses multiple routes of exposure

a? Other Biota
b?

1? Data document actual exposure
2? Analytical data sets are generally of high quality
3? Multiple routes of exposure are addressed
4? Broad coverage of phylogenetic groups (e.g., fish, shellfish, birds, wild mammals, reptiles, invertebrates, etc.), habitats, and environmental matrices
5? Information on various animal species will substantially enhance understanding of the phenomenon of human effects
6? Many monitoring programs are spatially and temporally replicated

a?
b? Limitations
c?
d? Human

19

e?

7? Adipose tissue monitoring looks for the "usual suspects"
8? Often fails to capture any short-lived compounds and rarely captures peak exposure
9? Limited number of compounds monitored
10? May not be representative with respect to time, population, or exposure distribution
11? May miss the disproportionately exposed or the particularly susceptible

a? Other Biota
b?

1? Limited number of compounds monitored – few potential endocrine disruptors monitored
2? "Exposure" or "potential exposure" are generally monitored; "biological effects" are not
3? Exposure to short-lived compounds is not monitored

a?

b? Guiding Principles for Using These Data for Priority Setting

c?

4? The greater the relevance of the data set to large populations, disproportionately exposed subpopulations, or particularly susceptible subpopulations, the more weight the data set should be given.

a?

5? Data sets with good quality assurance/quality control (QA/QC) data should be given greater weight than those data sets with lower QA/QC data.

a?

6? The lower the detection limits and the greater the efforts to test organisms that are likely to be exposed, the greater the weight "non-detect" data should be given. ~~"Non-detect" data should not be considered unless the detection limits are high and substantial efforts have been made to test organisms that are likely to have been exposed.~~

B. Environmental, Occupational, Consumer Product, and Food-Related Data

20

a?

b? Environmental, occupational, consumer product, and food-related data include data for chemicals in media to which humans and animals are exposed, including: 1) monitoring data for chemical contaminants found in a variety of environmental media such as water (surface, ground, and drinking); air, soil, sediment, food; and 2) use information for chemicals (e.g., cosmetics, and food additives such as those Generally Regarded As Safe (GRAS) under FDA law) found in consumer products and those chemicals likely to be internalized (i.e., taken into the body).

c?

d? Naturally occurring non-steroidal estrogenic compounds (NONEs) in food, including phytoestrogens and mycotoxins, are also included in this category. The benefits and potential hazards of NONEs to wildlife and humans have not been well characterized. A more detailed discussion is included in Section VIII.

e?

f? Strengths

g?

1? Provides data on likely exposures to humans and other biota

2? Databases exist for air, water, soil, and food

3? May be used to identify trends

4? Data can be used to identify relevant media for exposures (e.g., food, air, and/or water)

a?

b? Limitations

c?

5? Limited number of compounds monitored

6? Quantitative exposure levels must be inferred in many cases

7? "Detect" limits may vary from one data set to another

8? Use-data sources are not comprehensive, are frequently secondary sources, and may not be independently verified. The highest quality, most comprehensive data sources are usually maintained by fee-for-service organizations. Consequently, no use information databases for existing chemicals have been included in the EDPSD.

a?

b? Guiding Principles for Using These Data for Priority Setting

c?

21

9? The greater the relevance of the data set to large populations, subpopulations disproportionately exposed, or particularly susceptible sub-populations, the more weight the data set should be given.

a?

10? The more likely a chemical is to be internalized by an organism from its environment, the greater weight it should be given.

a?

11? Data sets with good QA/QC data should be given greater weight than those data sets with lower QA/QC data.

a?

12? The lower the detection limits and the greater the efforts to test organisms that are likely to be exposed, the greater the weight "non-detect" data should be given. ~~"Non-detect" data should not be considered unless the detection limits are high and substantial efforts have been made to test the media that are likely to be impacted.~~

a?

C. Environmental Releases

a?

b? Environmental release information includes data on chemicals with environmental releases to which humans and animals may be exposed, such as permitted industrial discharges to air or water and accidental release or spill data. An example of the industrial discharge data is the Toxic Release Inventory (TRI) reporting that is required by EPA. An example of accidental release or spill data is the Hazardous Substance Emergency Surveillance System maintained by the Agency for Toxic Substances and Disease Registry.

c?

d? <u>Strengths</u>

1? Provides data on potential and known exposures to humans and other biota
2? Databases exist for air and water
3? May be used to identify trends
4? Data can be used to identify relevant media for exposures (e.g., food, air, and/or water)
5? TRI is updated annually
6? Databases include location-specific data which are relevant to disproportionately exposed populations

a?

22

b? Limitations

1? Data exist for a limited number of industrial chemicals (528 in the case of the TRI)
2? Quantitative exposure levels are difficult to estimate in many cases
3? No data are available in the TRI for releases under 10,000 pounds per year

a?

b? Guiding Principles for Using These Data for Priority Setting

c?

4? The greater the relevance of the data set to large populations, subpopulations disproportionately exposed, or particularly susceptible subpopulations, the more weight the data should be given.

a?

5? The more likely the environmental releases are to lead to organism exposure, the greater weight the release data should be given (e.g., TRI releases to air and water should be given more weight than TRI releases to disposal such as permitted landfills, etc.).

a?

D. Production Volume Data

a?

b?
Production volume data includes production information, primarily volume, for chemical substances. Because of the nature of this information, it is mainly relevant to existing chemical substances. Such information can only be estimated for new products and is not relevant to environmental contaminants. The discussion of strengths and limitations which follows distinguishes between existing industrial (i.e., TSCA-regulated) chemicals and existing pesticides (i.e., FIFRA-regulated).

c?

d?
Strengths

e?

f? Existing Industrial Chemicals (TSCA-Regulated)

g?

1? Quick, easy way to obtain a rough estimate of exposure potential

23

2? Readily available (to EPA) for chemicals other than polymers and inorganics produced or imported in amounts greater than 10,000 pounds per year
3? Reliable and comprehensive
4? Identifies site-limited chemicals
5? Screens out non-isolated chemicals
6? Contains data on imported chemicals
a?

b? Existing Pesticides (FIFRA-Regulated)
c?
7? Production data available at national level (but not state level) for all covered products
8? Available to EPA and the public

a?
New Chemicals

a?
1? Estimated production volume data available to EPA for all new chemicals
2? Comprehensive
a?

b? Limitations
c?

d? Existing Industrial Chemicals (TSCA-Regulated)
e?
3? TSCA inventory update identifies site-limited intermediates, but does not contain information on uses of individual chemicals
4? TSCA inventory data may be protected as Confidential Business Information (CBI), which means that it is available to the EPA but not to the public
5? Does not contain data on degradates, mixtures of chemical substances, inorganics, polymers, or chemicals produced/imported in amounts less than 10,000 pounds per year
a?

b? Existing Pesticides (FIFRA-Regulated)
c?
6? Often lacking information on number of potentially exposed workers, fence-line concentrations, and environmental release pathways
7? Currently contains information on used products only
a?

b? New Chemicals

24

c?

8? TSCA data for new chemicals may be protected as CBI, which means that it is available to the EPA but not to the public

9? Production data are estimates

10? Many Pre-Manufacture Notifications (PMNs) are never commercialized; fewer are commercially successful

a?

b? Guiding Principles for Using These Data for Priority Setting

c?

11? Production volume provides only a very rough indication of potential human and ecological exposure. Combining production data with other data (e.g., effects data) minimizes, to a certain extent, some of the inherent weaknesses of using production data as a surrogate for exposure. Production information should not be used to prioritize between existing industrial chemicals and pesticides or between new chemicals and pesticides because production volume ranges are too divergent. For example, production volumes for high-volume industrial chemicals are several orders of magnitude higher than those for either new chemicals or pesticides.

a?

E. Fate and Transport Data and Models

a?

Environmental fate and transport information is available from various reference sources, including databases, textbooks, and monographs ((e.g., Swanson and Socha, 1997; Cowan *et al*., 1996). Although the data source matrix for environmental fate and transport data and models included in Appendix G highlights a number of specific sources of information, no single source is really superior to another in that each is a collection of data. Because there is a lot of environmental fate and transport data from which to choose, the challenge is to simplify the problem by identifying the critical fate and transport data for sorting and prioritization purposes.

a?

a?

The EDSTAC recommends that EPA focus on three subcategories of environmental fate and transport information: a) persistence; b) mobility; and c) bioaccumulation. Each of these factors can affect the bioavailability of a chemical substance because each is directly

25

correlated to potential exposure. The definitions used by the EDSTAC for these terms are as follows:

a?

a?

Persistence is the tendency of a chemical substance or its degradation products to persist (survive) in the environment without transformation into another chemical form.

a?

a?

Mobility is the tendency of a chemical substance to move within environmental media (e.g., air or water) or between media (e.g., to migrate from soil to groundwater).

a?

a?

Bioaccumulation is the capacity of a chemical to accumulate (be stored in the tissue) in an organism as a result of uptake from all environmental sources.

a?

a?

Strengths

a?

b?

Environmental fate and transport tests pertaining to the three categories are already in place and have a long history of use

1?

EPA has identified thresholds for various environmental fate and transport tests that trigger regulatory concern; however, at this time, the quantification of these potential thresholds (or "triggers") and their application to determine the potential for endocrine disruption may be lacking or subjective

1?

Modeling can also be used to estimate environmental fate and transport characteristics of persistence, bioaccumulation, and mobility when test data on specific substances are lacking

1?

a?

26

Limitations

a?

b?

No single source of information on fate and transport includes all chemical substances

1?

There are gaps in the data sources, making direct comparisons between chemical substances difficult

1?

Most fate and transport estimating procedures have not been validated over the range of possible chemical substances that will need to be considered for endocrine disruptor screening and testing

1?

Test data for the three selected parameters may not be available for all chemical substances

1?

At this time, there are no generally established or accepted environmental fate or transport criteria directly related to endocrine disruption

1?

Fate and transport of chemical substances may vary widely depending on environmental conditions; arbitrary standard conditions are established for regulatory and comparative purposes

1?

a? Guiding Principles for Using These Data for Priority Setting

b?

1? For each of the three environmental fate and transport characteristics – persistence, mobility, and bioaccumulation – the tables contained in Appendix H specify relevant physiochemical criteria along with their corresponding threshold (or "trigger"). These "triggers" are those which EPA generally takes into consideration when evaluating a pesticide or chemical for registration. However, it should be noted that EPA does not rely solely on "trigger" values, but considers other environmental effects (e.g., wildlife toxicology) before granting product registrations.

a?

2? The use of fate and transport data to help set priorities for T1S should take into account all three environmental compartments – air, water, and soil.

a?

27

3? Fate and transport characteristics should be based on laboratory or field tests where good quality data are unavailable. If laboratory or field data are lacking for a chemical, EPA should calculate the predicted fate and transport data for use in priority setting by means of reliable methodology or by use of an algorithm.

a?

4? The three environmental fate and transport characteristics identified above – persistence, mobility, and bioaccumulation – satisfied the above conditions. The physiochemical measures that are recommended for each of these characteristics are listed below:

a?

5? Hydrolysis half-life – persistence;
6? Biodegradation – persistence;
7? Photooxidation – persistence;
Volatility (Henry's Law) – mobility;

1?

Absorption Coefficient (K_{oc}) – mobility; and

1? Octanol: Water Partition Coefficient (K_{ow}/LogP) – mobility and bioaccumulation.

a?

b? Fate and transport measures that provided redundant information were eliminated. Some measures (e.g., photolysis) must be determined experimentally. A surrogate measure (in this case, photooxidation) can help to fill gaps in the data (photooxidation is one estimate of the atmospheric half-life of a parent compound due to reaction with photochemically-produced hydroxyl radicals).

a?

IV.
Effects-Related Information and Criteria

a?

b? In addition to HTPS, which is described separately in Section V., the effects-related information categories the EDSTAC recommends as the foundation for the priority setting

28

process include: a) toxicological laboratory studies and databases; b) epidemiological and field studies and databases; and c) predictive biological activity or effects models, commonly referred to as Structure Activity Relationship (SAR) and/or Quantitative Structure Activity Relationship (QSAR) models.

c?

d? Toxicological laboratory studies and databases include all published, publicly available, or otherwise useable information related to the laboratory study of toxic effects of chemical substances and mixtures on living organisms or cell systems, including humans, wildlife, and ecological systems.

e?

f? Epidemiological and field studies and databases range from hypothesis-generating descriptive studies, such as case reports and ecological analyses, to prospective cohort studies and rigorously controlled hypothesis-testing clinical trials or community interventions. The most common studies are descriptive.

g?

h? Empirical toxicological and epidemiological data are reported in a large number of peer reviewed scientific journals. Published studies are conducted with varying degrees of methodological rigor, and data are reported in widely varying detail. Consequently, information obtained from the general literature must be reviewed in considerable detail in order to determine its applicability and adherence to generally acceptable investigatory practices. Some positive reproductive effects data are included in several regularly updated databases which are described in more detail in Appendix G.

i?

j? Predictive biological activity or effects models attempt to identify correlation between properties that can be derived from the chemical structure or properties of molecules and biological activities, including those that can be identified through *in vitro* or *in vivo* screens and tests. SAR and QSAR models are also used to predict physiochemical properties such as solubility, volatility, and lipophilicity (LogP). QSARs are, in many ways, similar to modeling data and are most useful when empirical toxicological or epidemiological data are unavailable.

k?

l? General Guiding Principles for Effects-Related Criteria

m?

1? The EDSTAC believes that using published toxicological laboratory, epidemiological, or field studies for priority setting without first narrowing the universe of chemicals subject to detailed review would be virtually impossible in the appropriate time frame and with available resources. Accordingly, the EDSTAC recommends that data from the general scientific

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literature, which is not organized into logical databases, be used to help set priorities after an initial selection is made based on effects-related data organized into logical databases. This issue is discussed in more detail in Chapter Four, Section X. E.

a?

2? QSAR models should not "trump" HTPS information. Rather, HTPS data should be used to improve the QSAR database as described more fully in Chapter Four, Section V. G. 3.

a?

3? Positive epidemiological studies should be considered of higher value for priority setting purposes even in the presence of negative toxicological studies.

1? EPA has provided considerable guidance on how to interpret the results of toxicity, epidemiology, and other relevant data. This guidance should be relied upon in interpreting the available database for prioritizing effects information. The most relevant guidance for endocrine disruptor information are the Guidelines for Developmental Toxicity Risk Assessment (EPA, 1991) and the Guidelines for Reproductive Toxicity Risk Assessment (EPA, 1996).

a?

b?

EPA. 1991. Guidelines for Developmental Toxicity Risk Assessment. Fed. Reg. 56: 63798-63826.

c?

d? EPA 1996. Reproductive Toxicity Risk Assessment Guidelines, Fed. Reg. 61: 56273-56322.

e?

f? The remainder of this section describes in more detail the nature of the information included in each effects-related information category, the strengths and limitations of the type of information in each category, and a recommended set of guiding principles for how to use the information contained in each category to complete the task of setting priorities for endocrine disruptor screening and testing.

A. Toxicological Laboratory Studies and Databases

a?

b? Strengths

30

c?

1? For a few chemicals, particularly those regulated through FIFRA, a wide variety of whole animal studies have been completed using modern protocols with some endocrine sensitive endpoints (e.g., developmental toxicity, reproductive toxicity) and conducted under Good Laboratory Practices (GLPs)
2? Allows for testing of single agents and/or mixtures to establish cause-and-effect relationships
3? Studies are likely to provide useful dose-response data for the endpoints and species studied
4? Good coverage for a few chemicals and/or substances (e.g., petroleum crudes, organochlorine pesticides) with respect to aquatic species, birds, and wildlife

a? Limitations
b?

1? Toxicological database for industrial chemicals is less complete than that for pesticides
2? Ability to extrapolate endocrine-related knowledge in test species to other species, including humans, is limited by the lack of knowledge about interspecies comparative endocrinology
3? Effects at very low doses (i.e., inverted "U-shaped" dose-response curve or the "inverted J-shaped" curve indicative of hormesis) have generally not been examined in toxicological studies
4? Studies may not be designed to detect the relevant endpoints
5? Relevance of *in vitro* data to organisms and populations is not well characterized
6? Very little data on TSCA-related chemicals especially for effects on birds and fish
7? Little is known of endocrine disruptor effects in wild mammals, lower vertebrates, and invertebrates
8? Relatively few studies have looked at subtle and multi-generation effects

a? Guiding Principles for Using These Data for Priority Setting
b?

1? Whenever possible, *in vivo* studies with relevant endpoints and with wide dose-response data should be viewed as more relevant for priority setting than *in vitro* studies. This is especially true when considering *in vitro* studies featuring receptor-mediated mechanisms, which typically do not correlate well with endocrine-mediated *in vivo* effects.

a?

2? Studies that have any or all of the following characteristics should be valued greater than those that do not:

31

inclusion of relevant endpoints sensitive to endocrine disruption

1?

indication of a dose response for endocrine disruptor effects

1? receipt of peer review
2? GLP compliance

a?

B. Epidemiological and Field Studies and Databases

a?
b? Strengths
c?

1? These data may provide actual observation of impacts upon humans, organisms, or ecological communities, removing many of the uncertainties inherent in assessing risk based on laboratory studies
2? When these data include biomarkers of exposure or effects, they can serve to document a completed exposure pathway
3? Data from these studies can provide information on vulnerable populations or high-exposure subgroups, such as the occupationally exposed

a? Limitations
b?

1? Human disease and organ system dysfunction is multi-factor in causality, making it difficult to identify the contribution of individual factors unless they are dominant causes
2? The mechanisms which lead to specific human diseases are often unknown, and the specific endocrine disruption mechanisms which cause specific diseases are poorly understood
3? Epidemiological studies are statistically insensitive and able to detect only relatively high risks
4? Studies of highly exposed individuals may not be relevant to much lower population exposures or to more vulnerable subpopulations; extrapolation of high-exposure effects to low-exposure circumstances or between subpopulations introduces uncertainty and decreases the utility of the data
5? Studies often address only one route of exposure; this route may not be the most relevant route for the general population
6? Human and ecological communities are seldom exposed to only one compound; it is often impossible to examine the effects of multiple exposures and their possible interactions

32

a? Guiding Principles for Using These Data for Priority Setting
b?

1? Despite the many limitations inherent in epidemiological and field study data, statistically positive studies should be a priority indicator for additional screening and testing.

a?

2? When multiple studies exist, and there is a consistently positive association between exposure and an effect, but individually the studies do not reach statistical significance, this finding should be given weight when determining the priority for screening and testing.

a?

3? Weight given to statistically negative studies should be dependent upon the study design, quality of the data, and the power of the study to detect an effect. Negative human epidemiological studies and ecological field studies should be considered, but should not necessarily override positive toxicological studies when determining priority for screening and testing.

a?

4? When multiple studies exist, weight should be given to those studies that have received peer review and which are of high design quality. A checklist of issues important to evaluating a study should be developed to assist in the review. Such a checklist would include: likelihood of misclassification of exposure or disease; likelihood of introduction of bias; and utilization of standardized tools or methods.

a?

5? Descriptions of studies should include a characterization of their design. Study design is important in determining the inferences that can be drawn from the results. Commonly used descriptors include: descriptive (case reports, case series, calculations of rates of prevalence, incidence, mortality); observational (ecological, cross-sectional, case-control, cohort, proportionate morbidity/mortality ratio); and experimental (clinical trial, community trial).

a?

C. Predictive Biological Activity or Effects Models

a?
b? Strengths
c?

33

1? SARs/QSARs can be used to rapidly and relatively inexpensively predict biological activities of large numbers of compounds, thereby avoiding the need to prioritize on the basis of "no data"

2? Current SAR/QSAR models developed for application to endocrine disruption analysis predict binding affinity and, therefore, have the same advantages and disadvantages as the *in vitro* models upon which they are based

3? The use of SARs/QSARs in sorting and prioritizing allows for transparency and comparative consistency and avoids the problem of comparing different experimental data types against each other (e.g., two-generation study versus *in vitro* binding)

a? Limitations

b?

1? No models are perfect, and the current receptor binding models suffer both from the imperfections of receptor binding modeling and the ability of receptor binding to predict *in vivo* activity

2? Not all mechanisms of endocrine disruption are known or have enough data to model; it is, therefore, not possible to generate models for all possible ways in which the endocrine system can be disrupted

a?

b? Guiding Principles

c?

3? Guiding principles applicable to the biological effects used as the basis for the SAR, as well as to the QSAR itself, should be applied to the results of the SAR/QSAR.

a?

4? The applicable chemical domain of the SAR/QSAR should be as diverse as possible.

a?

5? SARs/QSARs should be developed using the most complete and accurate data sets available.

a?

6? SARs/QSARs should be validated and used only within the range of conditions for which they are validated.

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V.
High Throughput Pre-Screening

A. Introduction

During the course of its investigations the EDSTAC realized that, with the exception of food-use and consumer pesticides with regulatory mandates requiring two-generation developmental and reproductive testing, substantial endocrine effects data were lacking for most chemical substances. It is estimated that developmental and reproductive toxicity data are available in the literature for only 3,000 chemicals, a large fraction of which are pesticides and pharmaceuticals (*references to be inserted*). In addition, existing QSAR methods for endocrine-mediated effects are insufficiently advanced to be universally accepted as a source of effects data (*references to be inserted*).

In the absence of biological effects data, the scientists and officials within EPA charged with carrying out the priority setting process will be left with the choice of either raising or lowering the priority of a chemical based on a lack of information. Raising the priority seems to make sense from a public health protection standpoint, but in reality it will accomplish nothing because the vast majority of chemicals being evaluated are likely to be in the "no data" category for endocrine-mediated effects. In essence, if a lack of data became a rationale for making a chemical a high priority for screening and testing, it could render the biological effects portion of the prioritization process meaningless.

To address the problem of having little or no endocrine disruptor effects data on the vast majority of chemicals that will need to be screened and possibly tested, the EDSTAC recommends that EPA use "high throughput pre-screening" (HTPS). As the term is used throughout this document, HTPS refers to the use of automated processes (robots and specialized instrumentation) to aid in the screening of compounds. These automated processes involve a number of preparatory operations, some of which are also associated with traditional screening approaches, such as sample preparation (weighing and dissolving in the appropriate medium), screening, and the reading of screening results. However, in the case of HTPS, the process of placing the samples into a microliter plate, the sampling process itself, and the reading of sampling results, are all automated. Since all processes are automated and can be programmed to run continuously, in comparison to traditional hands-on or "bench" methods of screening, it is possible for large volumes of samples to be assayed in a relatively short period of time using this technology.

35

High throughput screening technology is used extensively in pharmaceutical and agrochemical industries to identify new chemicals as "discovery leads" or to identify chemicals substances that may have desirable or undesirable biological effects (*references to be inserted*). The EDSTAC proposes that high throughput screening technology be employed as a prioritization tool – hence the term "pre-screening" – for the endocrine disruptor screening and testing program. HTPS results, although limited in the scope of information they generate, will be useful in "flagging" a subset of chemicals as having an affinity for the estrogen, androgen, or thyroid hormone receptor. This information could be used in conjunction with other exposure- and effects-related information to determine the priority in which the chemical should be advanced to the screening and testing tiers of the program. It is important to note, however, that HTPS results will not be sufficient to make a definitive determination about whether a chemical does or does not have endocrine disrupting properties. This is the function of Tier 2 Testing.

The remainder of this section explains the purposes of HTPS and how it will be used to improve the endocrine disruptor priority setting and screening and testing processes. Chapter 5 describes the HTPS assays in more detail and their relation to the other assays in the Tier 1 Screening battery.

B. Purpose of HTPS

First and foremost, HTPS will provide a "level playing field." It will provide a baseline of systematically gathered data for the endocrine endpoints that are currently addressed in the program – estrogen, androgen, and thyroid. This is especially important for those chemicals for which such data on endocrine disruptor effects are otherwise lacking, namely most chemicals in the TSCA Inventory. The use of HTPS data should make screening more productive, as it is likely that a higher proportion of chemicals sent to T1S during the early phases of the program will have some evidence of biological activity.

Second, given the exploratory nature of HTPS, it is important to gain some perspective to interrelate the effectiveness of this methodology with other methodologies that can be used to identify compounds for screening such as QSARs. There is some concern that pre-screening chemical substances – especially some pesticides, for which substantial reproduction and developmental (whole animal) testing data already may exist – is a redundant exercise.

The EDSTAC recognizes that the inappropriate use of HTPS data could result in a certain stigma or in product de-selection. This potential is not unique to HTPS, but is a broader communication issue related to endocrine disruptor screens and tests in general. This issue is addressed in Chapter Six. EDSTAC members believe that if communication of the results of HTPS is handled effectively, inappropriate use of the data and potential adverse marketplace reactions to such inappropriate use will be minimized.

C. Which Assays Will Be Conducted in HTPS?

As noted in Chapter Two, one of the key mechanisms by which chemicals ~~can~~ affect the endocrine system is by interacting with the estrogen, androgen, or thyroid receptors. As discussed in Chapter Five, both the transcriptional activation and receptor binding assays are recommended for inclusion in the standardization and validation program for T1S. If ~~the~~ transcriptional activation assays can be standardized, ~~and~~ validated, and shown to be as reliable as receptor binding assays, the EDSTAC recommends that they~~it~~ be included in the ~~Tier 1 S~~screening battery as the preferred assay to detect receptor~~this~~ interactions. ~~Although t~~The receptor binding assay is an acceptable alternative that has decades of use, but may be less informative in terms of the nature of the interaction (agonism or antagonism) ~~it is less sensitive~~ than the transcriptional activation assays. The potential contributions of both types of assays in the context of priority setting are discussed below.

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The rReceptor binding assays areis a cell-free biochemical preparations in which one determines the amount of chemical thatwhich binds to the hormone receptor as a function of the concentration of the chemical in solution, thus determining the affinitypotency of the chemical foras a binder to the receptor. Because the receptor binding assay only measures binding, not the consequence of binding, one cannot know from this assay whether the substance would be an agonist (turn on or turn off gene expression like the natural ligand) or an antagonist, which has the ability to block the action of the natural hormone.hormone) or antagonist by blocking the natural hormone from reaching receptor sites. A second disadvantage of the receptor binding assay is that because it is a cell-free assay, it does not have the ability to metabolize chemical substances. Thirdly, receptor binding assays currently cannot be automated for high throughput application and must be run at the bench.

By contrast, the tTranscriptional activation assays areis conducted with intact cells that have been genetically modified to contain a hormone receptor andinclude a reporter gene. The reporter gene produces a protein that can be quantitatively measured to reflect the ability of a chemical to act like a hormone, or to block the action of a hormone.potency of a challenge toxicant to act as a hormone agonist or antagonist. The first step in transcription is binding of a natural hormone or hormone-like chemical substance to the receptor. Next The chemical may bind the receptor and the resulting the receptor-ligand complex binds to a specific place on the reporter gene called the hormone response element. In simple terms, the additional Subsequent steps include transcription of DNA on the gene to form RNA, and translation of the RNA to formsynthesize the marker protein. There are several different kinds of marker proteins that have been used in these assays; the common property is that they produce detectable signals that gene expression has taken place. For example, one marker protein, luciferase, is derived from fireflies and causes the emission of The assay keys on some property of the marker protein to indicate that receptor binding, and the subsequent events involving gene expression, have taken place. One transcriptional activation assay involves production of the enzyme luciferase, which causes the production of firefly light when acting on luciferin, which is introduced into the cell culture medium. Thus, the activity of a hormone mimic the chemical is actually detected by the amount of light produced by the cell. In practice, the amount of light produced can be by the substance being assayed is compared with that produced when by the natural hormone or a other reference substance is added to the culture.

Transcriptional activation assays incorporate receptor binding, but may be are more relevant to responses in living organisms than the receptor binding assays because they use involve wholeintact cells and measure also include the biological processes that are the result of receptor binding. This must be balanced with the fact that, because of the added complexity inherent in

these processes, it is possible for the marker protein to be expressed by actions of the chemical unrelated to receptor binding. ~~Since cells are involved, there is~~ The cells used may have some ability to metabolize tested chemicals. This metabolic competence can be enhanced by genetically incorporating the ability to make one or more of the enzymes typically involved in metabolism of exogenous chemicals~~and detoxification of chemicals~~. This may provide the assay with the ability to detect compounds which must be metabolically altered in order to bind to the receptor. These enzymes can also be added to the receptor binding assays. ~~Just as with the receptor binding assay, the ability to bind with the receptor can be obtained in the transcriptional activation assay.~~

Both~~In practice,~~ the transcriptional activation and receptor binding assays can be run automatically at several concentrations and the EC-50 (the concentration at which 50% response is obtained) can be determined. The EC-50 can be used to compare potencies of chemicals within each assay. It is therefore a useful index ~~tool~~ for setting priorities among chemicals for additional screening.

EPA has selected the transcriptional activation assay utilizing the luciferase reporter gene for demonstration purposes and, if shown to be practicable, intends to use it for the HTPS for existing chemical substances and mixtures. In this assay system the test material is run in the assays listed below with and without metabolic activation for agonist and antagonist potential. Multiple doses (probably five plus a control) would be run so that an EC-50 for transcriptional activation can be determined as a measure of potency as discussed above.

i? Estrogen Alpha Receptor Transcriptional Activation Assay (no metabolism)
ii? Estrogen Alpha Receptor Transcriptional Activation Assay (metabolism)
iii? Estrogen Beta Receptor Transcriptional Activation Assay (no metabolism)
iv? Estrogen Beta Receptor Transcriptional Activation Assay (metabolism)
v? Androgen Receptor Transcriptional Activation Assay (no metabolism)
vi? Androgen Receptor Transcriptional Activation Assay (metabolism)
vii? Thyroid Receptor Transcriptional Activation Assay (no metabolism)
viii? Thyroid Receptor Transcriptional Activation Assay (metabolism)

D. Limitations of the Assays to Be Conducted During HTPS

There are two noteworthy limitations to the types of assays being considered for the HTPS step. First, these assays cover only one of the possible mechanisms of action for endocrine-mediated toxic effects. At present, this includes biological activity resulting directly from the

binding of a chemical to the hormone receptor. Assays that assess the activity of enzymes involved in hormone synthesis are technically possible to conduct using high throughput technologies but are not being recommended for inclusion in the HTPS by the Committee. Despite this limitation, there are good scientific reasons to believe that most androgen- and estrogen-mediated toxicants capable of eliciting adverse effects at low doses do so by binding to a receptor. Therefore, the overarching goal of protecting human and ecological health is likely to be served by evaluating this mechanism early in the EDSTP.

The second significant limitation of the assays being considered for use in the HTPS step of the process is that they are unlikely to produce the same spectrum of metabolites that an intact animal produces. That is, chemicals that need to be metabolized to specific compounds in order to be active may not be detected by HTPS. Again, this limitation will be addressed in the screening tier. Both of these limitations will also need to be considered in the interpretation and utilization of the results of HTPS for purposes of priority setting.

E. Technical and Logistical Issues

Estimates of the speed of using high throughput technology are encouraging. Once the preliminary collection and handling of the chemicals are completed, it is not out of the question for several thousand assays to be run in one month, depending on whether confirmatory assays are also run (*references to be inserted*). However, there are technical and logistical constraints, as well as policy issues, that will need to be addressed in determining the number of chemicals that can or should be subjected to HTPS.

With regard to the technical constraints, some compounds have physical and/or chemical characteristics such as insolubility, high volatility, and high reactivity that are not amenable to any *in vitro* screening system, with or without the use of high throughput technologies. There are, however, scientific reasons to assume that highly insoluble and highly reactive chemicals are unlikely to be endocrine disruptors.

There are also some significant, but not insurmountable, logistical hurdles to be overcome. One of these includes validation of the assays for the significantly diverse kinds of chemicals that will be subjected to HTPS. While it is intended, and expected, that HTPS will provide false positives while minimizing false negatives, there is currently no history of use for HTPS methodology to evaluate large quantities of diverse chemical substances for potential endocrine disruption effects. Until now, HTPS endocrine assays have been used mainly as a

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tool to identify new leads or to increase biological activity of an existing lead. The possibility exists that HTPS may not provide sufficient effects data to warrant continued use, or that it may result in an unacceptable number of false negatives. However, all screens, whether automated or not, must undergo the process of validation.

In addition to validation, the problem of chemical procurement must be overcome before HTPS can be implemented. Procurement involves not only collection but quality assurance of the collected samples. Some chemicals in the environment (e.g., NONEs) are simply not commercially available. Moreover, since there is no registrant or chemical manufacturer, ownership and responsibility to shepherd such "orphan" chemical substances through the screening and testing processes ~~are issues that need to be addressed~~ will rest with EPA. Obviously, if chemical substances cannot be procured they must either be isolated or synthesized in order to be screened and, if necessary, tested. At this time, the EDSTAC is not aware of how many compounds could fall into this category.

EPA has launched a feasibility demonstration effort designed to ensure that the types of assays being considered for HTPS can be used on the wide range of chemicals that will need to be subjected to this step in the process. For more information on the HTPS feasibility demonstration project see Appendix I.

F. Which Chemicals Should Be Subjected to HTPS?

Although the use of robotic technology will greatly expand the throughput of chemicals over a given period of time for the selected assays, the EDSTAC is not recommending that all chemicals be subjected to HTPS which fall into the category of needing to be prioritized for T1S. Rather, the EDSTAC recommends that the set of chemicals (estimated to number approximately 15,000) currently produced in an amount equal to or greater than 10,000 pounds per year be subjected to HTPS. As indicated earlier in this report, the EDSTAC makes this recommendation in order to help EPA avoid a task that might never be completed if a higher number of chemicals were to be recommended for HTPS. The EDSTAC believes that 15,000 chemicals are not insignificant given the history of TSCA.

Chemicals prioritized for Phase I T1S which bypass the HTPS step because they are produced in amounts less than 10,000 pounds per year, would still need to complete the transcriptional activation assays contained in HTPS. Rather than doing so in the HTPS step, though, these lower production volume chemicals should be subjected to the same transcriptional activation assays contained in HTPS as part of T1S. ~~Chemicals not subjected to HTPS (because they are produced in amounts less than 10,000 pounds per year), but are selected for T1S during the first phase of the program, would still have to complete the transcriptional activation assays that will be conducted during the HTPS step.~~

The EDSTAC also recommends that chemicals permitted to bypass T1S and go directly to T2T, as well as those permitted to bypass both T1S and T2T and go directly to hazard assessment (due to functional equivalency of data), be subjected to HTPS. However, as described more fully below, the results of HTPS from these chemicals would not be used to set priorities for T1S. Rather, they will be used to develop QSARs and to inform dosing considerations and the types of tests that would need to be conducted in T2T.

G. How Will HTPS Results Be Used?

1. For Chemicals That Will Be Prioritized for T1S

In the context of setting priorities for T1S, the EDSTAC recommends that EPA use the results of HTPS in conjunction with other exposure- and effects-related priority setting information. In other words, HTPS results should be considered along with any other biological effects information that may be available, as well as information on exposure-related

considerations (e.g., biological sampling; environmental, occupation, consumer product, and food-related data; releases to the environment; production volumes; and fate and transport models and data).

It cannot be stressed enough that the HTPS results should not be regarded as definitively ruling in or ruling out endocrine-mediated toxicity. Such determinations can only be made with confidence at the end of the entire screening and testing process. There is concern that the results of HTPS will be over-interpreted because they are the first data that will be generated in the endocrine disruptor evaluation process. Therefore, it is important to stress the limitations of these assays. Most importantly, they are very simple *in vitro* assays. Like any *in vitro* method, the simplicity that makes the assays attractive for rapid generation of data also limits their reliability as predictors of what might occur in the intact organism. They do not possess all of the complexities of pharmaco-kinetics, pharmaco-dynamics, metabolism, and multi-system interactions that are inherent in the whole organism. It is rare for an *in vitro* assay for any toxicity to have better than an 80% concordance with *in vivo* results. For this reason, most *in vitro* assays are used only as a preliminary step of a more comprehensive assessment.

Therefore, it will be important to keep in mind that the results of HTPS will primarily be useful as a pre-screen to indicate the need for further evaluation, but will not always be predictive of true potential for toxicity. The results will be useful in the context of the remainder of screening (and testing, if a compound proceeds that far) in interpreting the potential of a chemical to evoke endocrine-mediated responses. For these reasons, the EDSTAC strongly recommends that a negative HTPS result not be used as a basis for placing a chemical into the "hold box." Further, the Committee recommends that a negative HTPS result not be used, in isolation, to decrease the priority of a chemical for screening and testing; nor should a positive HTPS result be the only factor considered in setting priorities for T1S. |

2. <u>For Chemicals That Meet the Criteria for Going Directly to T2T or Hazard Assessment</u>

Chemicals that meet the criteria for proceeding directly to T2T or hazard assessment would also be subjected to HTPS according to the EDSTP. However, unlike the large number of chemicals that do not meet these criteria, the results of HTPS from this set of chemicals will <u>not</u> be used to help set priorities for T1S. Rather, the results will be used for two purposes:

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i? to help improve the development of QSARs; and
ii? to inform the types of endpoints to be evaluated and any additional assays to be conducted as part of T2T.

There may be some concern about the redundancy of subjecting pesticides and other chemicals for which substantial two-generation reproductive and developmental (whole animal) testing data already exists. However, the EDSTAC believes the value of generating data that can be used to refine and develop robust estrogen, androgen, and thyroid predictive molecular modeling tools (e.g., QSARs), outweighs the relatively low cost associated with subjecting these chemicals to HTPS.

3. To Improve QSARs

The EDSTAC recommends that existing QSAR models be rederived and supplemented with data from the HTPS assays, thereby expanding the predictive ability of these models. Thus, when it comes time to set priorities for the first phase of T1S, HTPS data, as well as improved QSARs, should be used along with other relevant exposure and effects data.

It is envisioned that the process of QSAR model expansion and improvement will then continue in a cyclical feedback manner, thus providing the opportunity to validate evolving QSAR models using external data sets for screens and tests of compounds not subjected to HTPS. Eventually, predictions of endocrine disruption potential obtained from validated QSAR models could be used as surrogates for HTPS data in the case of compounds where effects data are not available.

H. Practical Considerations and Constraints to Be Considered in HTPS Implementation

There is widespread agreement that several practical considerations will need to be addressed for HTPS to work as intended. These include:

1? Demonstrating the feasibility of HTPS – An important first step in implementing the recommendation of the EDSTAC to incorporate the use of HTPS into the EDSTP is to undertake an effort to demonstrate the feasibility of using this technology for the wide range of chemicals that will need to be considered for endocrine disruptor screening and testing.

2?

1? Collecting, handling, and QA/QC of the chemicals to be tested – The procurement of sufficient quantities of relevant chemical substances, the shipment of these materials, and the assurance of the chemical identity and purity of these chemicals will be the most time consuming phase of HTPS. While these issues are inherent in any of the assays being considered for screening or testing, they must be taken into consideration when planning for HTPS, as they are likely to contribute to the cost and time for this step of the program. The EDSTAC recommends that EPA explore the feasibility of creating an archive of a subset of these chemicals, which can be accessed by researchers interested in studying endocrine-

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| mediated toxicity or in validating new screens for endocrine disruptors. This may be
| particularly important for radio labeled compounds that are costly to synthesize. There is
| precedence for such activities, including the EPA Pesticide Repository, the National Institute
| of Standards and Technology (formerly the Bureau of Standards) in the Department of
| Commerce, and the NTP chemical repository for the validation of *in vitro* developmental
| toxicity.

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2? Patent issues – Many or all of the HTPS under consideration are patented. However, it should be noted that intellectual property is an issue that must be addressed before implementing any endocrine disruptor screening and testing program. This is unlikely to be a critical issue for a massive screening effort because it is almost certain that such work would be done under contract by the holder of the patent. It may, however, be a significant issue for individual investigators or companies who wish to work with the assays on an investigative basis in their own laboratories. Licensing agreements should be worked out before any final decisions are made.

a?

3? Overall costs and specific cost factors – As with all screening assays, the cost of performing an assay needs to be taken into account in selecting which HTPS assays to recommend, as high cost may limit the number of chemicals that can be evaluated.

a?

4? Validation of the HTPS assays for the wide range of chemicals that are intended for pre-screening – High throughput screening technology has been used in the pharmaceutical and agrochemical industries to find chemicals with novel and relevant biological activity, as these are the ones that are likely to be candidates for lead optimization. However, chemicals that have been identified so far as having endocrine-mediated effects typically have low potency. Questions such as: How good will the assays be at detecting these?; What is the limit of detection?; and How easily will these assays accommodate a range of chemical properties, such as solubility, pH, high vapor pressure? can be addressed, but doing so may require some research involving a representative group of chemicals before HTPS can be implemented on a large scale. Based on the results of using HTPS as a tool for identifying discovery leads, one generally should expect a "hit rate" of 1.8-2.0% for a very weak lead (activity at 100 uM), 0.6% for a weak lead (activity at 10 uM), and 0.15% for an average lead (1 uM).

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b? Other implementation issues, such as who will be responsible for conducting various parts of the HTPS process, how much each step will cost, etc., are not addressed in this document. However, it is envisioned that EPA will undertake the coordination and expense of conducting the HTPS

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step of the program. It is also assumed that implementing the HTPS process will require EPA to work cooperatively with industry to collect what will be a very large number of chemical samples. Moreover, the issue of "orphan chemicals" – those for which there is no current manufacturer or registrant – is an issue that EPA must address.

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VI.
Recommendations for Handling Polymers

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b?

A. Introduction

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b? This section presents some key issues associated with the prioritization of polymers for endocrine disruptor screening and testing along with several options and a recommended approach for how polymers should be treated.

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1. Chemical Nature of Polymers

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b? Polymers are defined in 40 Code of Federal Regulations (CFR) Part 723 as

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> "a chemical substance consisting of one or more types of monomer units and comprising a simple weight majority of molecules containing at least three monomer units which are covalently bound to at least one other monomer unit or other reactant and which consists of less than a simple weight majority of molecules of the same molecular weight. Such molecules must be distributed over a range of molecular weights wherein differences in the molecular weight are primarily attributable to differences in the number of monomer units."

a?

b? Polymers result from chemical reactions that permit varying numbers of monomers or monomer units and other precursors to be chemically incorporated into the products of the reactions. According to 40 CFR Part 723, the term "monomer unit" means "the reacted form

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of the monomer in a polymer" (i.e., the monomer must have formed at least one covalent bond with another like or unlike molecule under the conditions of the relevant polymer-forming reaction).

c?

d? Polymer molecules typically vary in their degree of polymerization, or the extent to which they have incorporated varying numbers of monomers, oligomers, and other precursors. However, polymer products might be composed of various other substances that usually are not the result of the polymerization reaction including:

e?

1? Residuals – unreacted polymer precursors, monomers, and other reactants
2? Byproducts – catalyst residues, free-radical initiator byproducts, etc.
3? Impurities – precursor impurities, oxidation products, etc.
4? Other substances – those that are mixed into the product, such as fire retardants, plasticizers, solvents, inhibitors, fillers, colorants, antioxidants, slip agents, etc.

2. Present Regulatory Status of Polymers

a?

b? The initial TSCA Inventory (or Initial Inventory), published in 1979, consisted of those chemicals that were manufactured in the U.S. or imported into the U.S. on or after January 1, 1975, and before the end of the initial reporting period (which varied depending on the chemical and/or company circumstances). Certain allowances were made for later additions and corrections. The Initial Inventory contained about 60,000 chemicals, approximately half of which were polymers. Chemicals on the Initial Inventory are referred to as "existing chemicals." Chemicals not on the Initial Inventory are considered "new" and are subject to the Pre- Manufacture Notification (PMN) requirements of TSCA. After EPA completes the pre-manufacture review of a new chemical and when the manufacturer or importer of the chemical notifies the Agency that manufacture or importation has commenced, EPA adds the new chemical to the Inventory.

c?

d? The existing chemical polymers are described in the Initial Inventory using a simplified procedure for naming the polymers. Polymers on the Initial Inventory are named as "Polymer of A, B, C, D..." where A, B, C, D... are the monomers which are reacted to form the polymer. The Inventory chemical name does not include any description of the chemical identity of the specific polymer or polymers that are made from these monomers.

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For example, there is no information about whether the polymer is in the form of a carbamate, amide, isocyanate, or some combination of these functional groups; nor is there any mention of the presence or absence of reactive functional groups, such as isocyanate or epoxy groups. In addition, the number average molecular weight (NAMW) – which refers to the arithmetic average (mean) of the molecular weight of all molecules in the polymer – distribution of the polymer or polymers made from the listed monomers is not reported. The Initial Inventory, however, does include a number of low NAMW oligomers (dimers, trimers, etc.) which are purposefully manufactured as such.

e?

f? In contrast to the estimated 30,000 polymers reported on the Initial Inventory (John Walker, U.S. EPA, personal communication), new chemical polymers that are reported to EPA include a chemical description of the polymer containing information on the NAMW distribution, the presence of reactive functional groups, etc. In addition, EPA receives information on the anticipated uses, exposures (occupational, environmental, consumer, etc.), and environmental releases of the new polymer.

g?

h? The EPA under TSCA first proposed the exemption of certain polymers (NAMW greater than 20,000 daltons) from pre-manufacture notification in 1982 (47 Fed. Reg.). The Final Rule for this early exemption was published in 1984. In making its no-risk finding, EPA concluded with regard to polymers that:

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"Molecular weight is clearly the prime determinant of risk. For a chemical to elicit a toxic response within an organism, it must come into direct contact with the biological cells from which it elicits the response. Because all organisms are encased in protective membranes, a chemical must penetrate these membranes and be translocated to various parts of the organism to gain access to its target sites. If a chemical cannot penetrate the protective membranes to access a target site, and it cannot elicit a toxic response, it will not generally present a risk." (49 Fed. Reg. 46081, also cited in 60 Fed. Reg. 16328)

k?

l? EPA operated with this exemption for almost a decade until a proposal to expand the exemption was made in 1993 (58 Fed. Reg.). That proposal was published as a final rule in 1995, and it sets out the exemption policy under which the TSCA program now operates (60 Fed. Reg.). EPA extensively reviewed over 10,000 polymers from 1980 to 1995 and concluded that:

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"Of these 10,000, the polymers that would have qualified under the final polymer exemption rule [1995] have consistently been characterized as posing low concern for both adverse health and environmental risks by the Agency during the course of PMN review. The characteristics of a significant number of polymers (i.e., their NAMW and/or physical/chemical properties) are such that they are neither absorbed by biological systems nor do they interact with biological systems, as described above." (60 Fed. Reg. 16329)

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p? As required by section 5(h)(4) of TSCA, the current polymer exemption is based wholly on a finding by the EPA that the:

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"manufacture, processing, distribution in commerce, use, and disposal of new chemical substances meeting the revised polymer exemption criteria will not present an unreasonable risk of injury to human health or the environment under the terms of the exemption." (60 Fed. Reg. 16316)

s?

t? The present regulation (60 Fed. Reg. 16333) exempts:

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1? polymers with average NAMW between 1,000 and 10,000 daltons if they do not contain other than certain specified reactive functional groups (as well as containing less than 10% oligomers with NAMW less than 500 daltons and less than 25% oligomers with NAMW less than 1,000 daltons);

2? polymers with average NAMW greater than 10,000 daltons (and less than 2% oligomers with NAMW less than 500 daltons and less than 5% oligomers with NAMW less than 1,000 daltons);

3? polyester polymers made with any of a long list of specified reactants; and

4? polymers produced in quantities less than 10,000 kilograms per year.

a? Polymers that are **ineligible** for the exemption include:

1? polymers that degrade, decompose, or depolymerize;

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2? polymers that are prepared from monomers or other reactants that are not on the TSCA Inventory; and
3? water-absorbing polymers with NAMW greater than or equal to 10,000 daltons.

B. Key Issues Associated with the Prioritization of Polymers

a?

b? The PSWG considered exempting from priority setting for endocrine disruptor screening and testing polymers with a NAMW greater than 1,000 daltons, a designation similar to the cutoff for reporting which exists for new chemical polymers under TSCA. All polymers with a NAMW less than 1,000 daltons would be treated like all other chemicals and would be subjected to priority setting. The polymers treated as exempt would be put into a "hold box" pending knowledge about the likelihood of monomers or other low NAMW polymers leaching out, and pending screening and testing data about the monomers themselves. However, continued examination by the PSWG surfaced concerns in several areas.

c?

d? <u>Bioaccumulation/Potential Exposure</u> – The basis for the original proposal to exempt polymers was the assumption that molecules larger than 1,000 daltons would be too big to cross biological membranes and barriers. More detailed examination revealed that, because of delayed intestinal closure in humans and other animals (*references to be inserted*), it is conceivable that, if a neonate was orally exposed to a polymer with a NAMW greater than 1,000 daltons, some of the polymer could enter the body and interact with the cell. Such an interaction is unlikely to occur in a more mature animal. Gastrointestinal absorption is dependent on factors such as lipophilicity, molecular weight, particle size, and metabolism of chemicals in the gastrointestinal tract (*references to be inserted*).

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f? The potential for gastrointestinal absorption of high molecular weight substances was taken into consideration by the EPA as early as 1982. The Agency concluded that:

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Substances with NAMW greater than 1,000 daltons are generally not readily absorbed through the intact gastrointestinal tract. (49 Fed. Reg. 46081);

1? "For a chemical to elicit a toxic response within an organism, it must come into direct contact with the biological cells from which it elicits the response. Because all organisms

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are encased in protective membranes, a chemical must penetrate these membranes and be translocated to various parts of the organism to gain access to its target sites. If a chemical cannot penetrate the protective membranes to access a target site, and it cannot elicit a toxic response, it will not generally present a risk." (49 Fed. Reg. 46081, also cited in 60 Fed. Reg. 16328)

Dermal exposure, rather than inhalation or ingestion, is the major route of exposure for most polymers. (47 Fed. Reg. 33930)

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b? Based on the data available, EPA was able to proceed in making its no-risk finding as a basis for the polymer exemption.

c?

d? The physical properties of a polymer affect not only its functional ability, but its fate and transport in the environment. Generally, as the molecular weight and degree of polymerization increase, the affinity for adsorption to solids (soil and sediment) increases and the potential for biodegradation and bioaccumulation decreases. ~~As mobility in the environment decreases, the likelihood of exposure decreases.~~ (*references to be inserted*)

e?

f? Polymer Complexity – Polymers are complex substances consisting of additives such as fire retardants, antioxidants, slip agents, colorants, residual monomers, catalysts, additive reaction products, catalyst residues and reaction products, byproducts, low molecular weight polymer chains, etc. Although additives, monomers, catalysts, many oligomers, and many other substances will be included in the priority setting scheme, some of the other polymer components may not be. Concern about their toxicity arose on the part of the PSWG after reviewing some work done in the early 1970's on a complex polymer fluid showing that the fluid's polysiloxane dimers and trimers were more toxic components of the mixture than were the monomers. Although the issue was not one of incomplete breakdown products, but rather of intentionally made dimers and trimers, the work highlighted the fact that by only studying the monomer, it is conceivable that one might miss a higher order of toxicity reached in the dimers, trimers, etc. The toxicity of these other polymer components may not be the same as the toxicity of the monomers. Thus, testing data from the monomers and additives may not provide complete guidance as to the toxicity of the entire polymer.

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h? Composition of Copolymers – Most polymers, for regulatory purposes, are described and assigned Chemical Abstracts Service Registry Numbers (CASRNs) on the basis of the monomers used in their manufacture. For polymers having multiple monomers (or

copolymers, as opposed to homopolymers), the relative concentrations of the various monomers can vary widely, but the polymers can still be assigned the same CASRN. For example, poly(A/B) with an A/B ratio of 95/5 or 5/95 is still described by the same CASRN. Consequently, for purposes of prioritizing polymers for testing, the CASRN does not represent a unique chemical composition.

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j? In addition, for many condensation polymers, chemically identical polymers can be made from slightly different monomers. In this instance, the CASRN would be different, even though the polymers are compositionally indistinguishable.

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l? The variable compositions within a CASRN listing, and identical compositions for different CASRN listings, are problematic for both new polymers, as well as for those nominated to the original Inventory.

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n? Testing of Polymers – Many polymer components do not have an identity apart from their role as a component of a polymer. Hence, they do not exist independently and, in general, cannot be readily synthesized or purified for screening and testing. If such components were to be tested, they would have to be extracted from the polymer matrix in which they exist. Such an extraction would be a highly complex undertaking, requiring the identification of a long list of parameters such as:

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1? solvent for the extraction;
2? time for the extraction;
3? temperature for the extraction;
4? surface area of the polymer to be extracted; and
5? volume of the extracting solvent.

Varying any of these parameters would affect which polymer components are extracted and how much of any component is extracted. Variation in these parameters can reflect different use conditions of the polymer, different potential exposure conditions, different properties of the polymer, and different components which one desires to extract. In addition, any extraction would yield an extract which is a mixture consisting of the polymer components, primarily the smaller monomer and additive compounds. Thus, any test will yield a result which does not describe the endocrine behavior of the polymer components by themselves. Further, since the conditions of the extraction determine the composition of the extract and the concentration of the components in the extract, the test

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may not necessarily yield useful information regarding the potential toxicity of the polymer.

Once the polymer components are extracted, the extract may need to be concentrated, for example, to obtain an appropriate concentration for testing or to remove extracting solvents. This "concentration" step must be very carefully conducted so as to ensure that no part of the extract is lost or altered. In most cases, validation of this step would be very difficult.

[NOTE TO THE READER: The following two subsections contain new text that was presented and agreed to at the March plenary as a complete replacement for prior text. Underlines and strikeouts for these two sections are not indicated.]

Migration of Polymer Components

Two types of components are of interest: 1) the lower molecular weight monomers and oligomers that may be present in the matrix of high NAMW polymers; and 2) the additives, catalysts, etc. Because essentially all of these components are on the TSCA Inventory, they will be considered along with other chemicals during prioritization and will receive due consideration for screening and testing.

Degradation Products of Polymers

The EDSTAC considered the issue of the potential for polymers to degrade in the environment and pose risk of exposure to substances which would not be captured under the priority setting scheme. Most polymers are chemically designed to be used in applications where stability is essential to their functional and commercial success. Although most polymers would not be expected to degrade in the environment, data are not complete for all polymer classes. However, concern about the ability of chemical degradates to enter the environments, especially water, is not limited to the potential degradates of polymers alone, but includes essentially all chemicals which are released to the environment. The EDSTAC does not consider it necessary to give special consideration to the potential degradates of polymers. These issues will be considered for polymers as wells as other chemicals in the priority setting scheme in the context of the exposure criteria.

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C.
Options Considered by the PSWG

1. Include All Polymers (Regardless of NAMW) from Priority Setting

This option would ensure, in theory, that no molecules are overlooked in priority setting. The polymers would be subject to the same exposure- and toxic effects-related criteria as are the smaller molecules. From a practical standpoint, however, exposure data would be the primary driver in this application, and such data would be hard to obtain for most of the polymers.

Moreover, it is expected that for most polymers, actual exposure to humans and other animals (of any age) would be very small. Considering the primary concern of the PSWG related to exposure of human neonates, a high percentage of polymers would likely present no exposure to such populations. Therefore, the public health value of including all polymers in the prioritization exercise would be negligible. This needs to be balanced in light of the significant resources that would be required to actually characterize the polymeric substance, obtain and evaluate the available exposure and effects data, and make a prioritization decision for thousands of polymers.

2. Include Polymers with NAMW Greater than 1,000 Daltons to Which Neonates Are Likely to Be Exposed; Put the Others in Hold

Criteria would need to be developed to identify those polymers which are used in materials most likely to come in contact with neonates. It must be acknowledged that such criteria are most workable for humans and less readily ascertainable for fish and wildlife. Examples of the kinds of polymers that would need to be considered include those used in food contact materials, infant toys, etc. A significant advantage of such an effort over option number 1 would be to focus the priority setting on those molecules most likely to present a potential exposure to the sensitive population. The technical difficulties associated with screening and testing polymers, which are described above, would still remain.

3. Hold Polymers with NAMW Greater than 1,000 Daltons from Priority Setting

No priority setting of the polymer would occur unless data indicates leachable monomers or oligomers have endocrine disruption potential. This option focuses resources on the polymers

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that contain or might release monomers or oligomers of concern. This still entails a significant technical investment to determine the nature and amount of leachable "other components" from the polymer. Priority setting would initially take place on the monomers under the same criteria as other single chemicals.

4. Exempt All Polymers with NAMW Greater than 1,000 Daltons; Concentrate on Monomers

This option obviates the resource-intensive step of considering the "other" chemicals present in a typical polymer mixture. Priority setting would take place on the monomers and the appropriate ones would be screened and tested. This is the least resource-intensive option (at the priority setting stage, at least) and focuses on identification of monomers of concern. Concerns about a monomer's use in a polymer arise not during priority setting, but rather in the risk assessment phase of the program. It would be at this point that the results of screens and tests, along with the proper dose-response analysis, would be considered in light of exposure assessment (including use and migration from polymers) to form a risk assessment. It is important to note that this option would still require detailed consideration of polymers, but at a later stage in the program and only for those polymers for which screening and testing of the monomer indicate a concern.

5. Modified Option 4 – Treat Polymers as Mixtures and Consider Them Along with Other Mixtures

The issues that complicate the consideration of polymers are similar, if not identical, to those faced by mixtures in general. These include: often broadly defined composition; wide range of chemicals present in one CASRN (chemical nature and NAMWs); etc. By considering polymers along with mixtures, the same consideration of exposure- and toxic effects-related criteria would have to occur as with other mixtures.

D.
Recommendation for Handling Polymers

The EDSTAC prefers option number 3. In particular, the EDSTAC recommends that existing and new chemical monomers and oligomers, as well as new chemical polymers with a NAMW of less than 1,000 daltons, should be considered within the broader priority setting scheme and undergo screening and testing as appropriate. It is

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important to point out that the priority setting scheme will consider the potential for sensitive populations to be exposed (e.g., the exposure of neonates). Existing chemical polymers are viewed as presenting a lower priority for initial action because of the unavailability of critical information such as NAMW and explicit information about the chemical nature of the polymer. In addition, because it is likely that many of the existing polymers are very large molecules (NAMW greater than 50,000 daltons), there is limited potential for exposure to residual monomers and low molecular weight oligomers contained in existing polymers. ~~As noted above, the EDSTAC recommends the 300+ chemicals on the EPA SDWA List of Chemicals of Concern (EXACT REFERENCE TO BE PROVIDED) be used to identify the potential degradates of polymers that are most likely to present an environmental exposure and should, therefore, be subjected to endocrine disruptor screening and testing in accordance with the priority setting process recommended in Chapter 4, Section XI.~~

Thus, the EDSTAC recommends:

i? All monomer and oligomer components of polymers should be prioritized for and subjected to endocrine disruptor screening and testing.

i? All "new" polymers (i.e., those produced after the Initial Inventory, which was published in 1979) with a NAMW less than 1,000 daltons should also be prioritized for and subjected to endocrine disruptor screening and testing.

a?

i? All previously manufactured polymers and all "new" polymers with a NAMW greater than 1,000 daltons should be set aside pending the outcome of the screening and testing of their monomer and oligomer components.

i? If the component is determined to have endocrine disrupting properties, the component should proceed to hazard assessment.

a?

As with any chemical shown to have endocrine disrupting properties, an exposure~~ risk~~ assessment will be performed. ~~Although discussion of the specifics of risk assessment is outside of the purview of the EDSTAC, it is important to note that, in addition to the~~

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~~hazard assessment referred to in recommendation number 4 above, an exposure assessment for the component will be conducted.~~ It is at this stage that all potential exposure routes for a component would be determined, including the potential for the component to be available from the polymer.

Finally, the EDSTAC recommends that EPA gain experience with monomers, oligomers, and new polymers with NAMW less than 1,000 daltons and learn how to apply that experience toward the development of an approach to address existing polymers. This would focus the endocrine disruptor screening and testing program on the polymers about which the best information is available and on those most biologically relevant to the endpoints of concern. To the extent that data generated during implementation of the EDSTP on new chemical polymers indicate a problem, EPA should obtain information on molecular weight, production volume, chemical identity, and any other appropriate information needed to identify and evaluate existing chemical polymers in the priority setting step of the EDSTP. This could be done through the TSCA Inventory Update Rule.

VII.
Recommendations for Handling Mixtures

A. Introduction

The EDSTAC has acknowledged the importance of considering mixtures, and public comment at plenary meetings reinforced the Committee's concern over mixtures. Regulators around the world have made many attempts to deal with the toxicity of mixtures, with endpoints other than endocrine disruption in mind (*references to be inserted*). Many of these efforts have become stalled due to the enormity of the job. This section discusses several of the key issues relating to establishing priorities for the screening and testing of chemical mixtures for endocrine disruption and presents a scheme for organizing the various mixtures, recommended priority setting criteria, and recommendations for initial action.

B. Definition

Quite simply, a mixture is any combination of two or more chemicals. The number of mixtures present in the environment is practically infinite. In addition to the approximately

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75,000 chemicals on the TSCA Inventory, many other metabolites, degradates, and combustion products may be found as well. Given this huge array of possible mixtures, we should focus on the grouping of mixtures into general classes.

C. Categorization Scheme for Mixtures

Mixtures can be organized based on where they are found in the environment, their source, and their chemical makeup. The EDSTAC proposes a categorization scheme that spans the range from mixtures found in products, through mixtures found in the environment, to mixtures detected in human tissues. One way to think of this spectrum is as a potential exposure "chain." The presence of a mixture in a product merely indicates that *if* a product is used in a certain manner and an organism is present during or after use, the potential for exposure exists. Detection of a mixture in environmental media indicates that the mixture is present in the environment in which organisms live and that exposure is possible. At the far end of the exposure spectrum is the detection of mixtures via biomonitoring studies in animal tissues. Such detection indicates that exposure has actually occurred. The proposed scheme for organizing mixtures, along with examples of categories of data that fit, is outlined below:

1. Products commonly containing mixtures

   i? Pesticide formulations
   ii? Cosmetics, toiletries, cleaners, other consumer products
   iii? Petroleum derived products – gasoline, solvents, metalworking fluids
   iv? Food – including additives, contaminants, phytoestrogens
   v? Pharmaceuticals/over-the-counter drugs
   vi? Other commercial, formulated products

   For products commonly containing mixtures, a further three-part distinction can be made between:

   1? Formulated products – products mixed to contain a specified proportion of chemicals necessary for product function. Examples include pesticides, cosmetics, medicines, etc.
   a?

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2? Commercial non-formulated products – products which are blended to attain certain performance criteria. In contrast to the formulated products, the proportion of ingredients is generally not fixed. Although knowledge about the precise identity or proportion of the chemicals contained therein is limited, some information about the chemical nature (e.g., aliphatic/aromatic) is available. Examples include fuels, solvents, and lubricants.

a?

3? Industrial chemicals – For the purposes of priority setting, these will be considered as single chemicals. However, even though one chemical predominates, other chemical impurities may be present as well. The potential activity of impurities must be considered in the screening and testing of these "single chemicals." Commodity chemicals such as styrene, propylene, and toluene are examples of such "single chemicals."

2. Environmental media commonly containing mixtures (including, but not limited to, TSCA chemicals, metabolites, degradates, and combustion products)

   a. Contaminated media at Superfund sites
   b. Toxic chemicals in urban air
   c. Contaminated drinking water
      i. Pesticides/fertilizers
      ii. Disinfection byproducts
      iii. Chemicals commonly found in drinking water
   d. Surface water and groundwater
      i. Effluents
   e. Indoor air
   f. Sediments/sludge
   g. Occupational media (e.g., welding fumes, coke oven emissions, etc.)

3. Tissues and media from humans and other animals (including animals produced for food, fish, and wildlife) commonly containing mixtures (including, but not limited to, TSCA chemicals, metabolites, degradates, and combustion products) from:

   i? Blood

   ii? Breast milk

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iii? Exhaled breath
iv? Fat
v? Urine
vi? Miscellaneous tissues (e.g., finfish, shellfish, meat, poultry, etc.)

D. Determining the Composition of Mixtures to Be Considered~~Examined~~

Determining the precise composition of mixtures to be considered for prioritization is challenging given the large number of possibilities. This task is somewhat easier for mixtures found in products because the basic formulations are usually well defined and are not likely to drift widely over time. However, the composition of mixtures found in environmental and biological samples is highly variable with respect to specific components present and their relative amounts. In such cases, higher priority should be given to mixture combinations typically or frequently found in environmental and biological media.

E. Criteria for Prioritizing Mixtures

The following are some recommended criteria for prioritizing mixtures for the purpose of endocrine disruptor screening and testing:

1. Exposure data on mixture (same criteria as with single chemicals)

1? Biological sampling (human and other biota) data for components of mixtures
2? Environmental, occupational , consumer product, and food-related data
3? Environmental releases
4? Production volume
5? Fate and transport data and models

a?

b? 2. <u>Toxic effects associated with the mixture in question</u> (same criteria as with single chemicals)

6? Toxicological laboratory studies and databases
7? Epidemiological and field studies and databases (populations affected)
8? Predictive biological activity or effects models (e.g., QSARs)

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a? 3. Toxic effects data on major components

1? Use the ranking developed for individual components by the EDSTAC to rank mixtures based on the relative ranking of the components they contain

2? This approach is especially useful for:

3? mixtures for which there are no toxic effects data on the mixture itself. If toxic effects data are available on the mixture, those data should be given primary consideration in priority setting for the mixture.

4? environmental contaminants and complex product mixtures, especially if the mixture contains a component with a high priority for screening and testing.

a?

F. Recommendations

a?

b?

The EDSTAC and EPA are, in many ways, entering uncharted territory. The evaluation (including the design, implementation, and interpretation of screens and tests) of the potential for endocrine disruption of *single compounds* is still
| emerging and fraught with much scientific uncertainty. Nonetheless, the
| Committee urges EPA to rigorously address the science of mixture toxicology
| in their research efforts, and recognizes the need, under the auspices of the
| EDSTP, to begin to confront mixtures.

c?

d?

| ~~Similarly, t~~The science of the evaluating mixtures remains complex and unclear for *any* toxic endpoint. Given the potentially overwhelming task of establishing priorities for endocrine disruptor screening and testing of mixtures, we recommend a well-considered, step-wise approach to the inclusion and prioritization of mixtures in the screening and testing program. ~~Although the issues of risk assessment and risk management are beyond the scope of the EDSTAC, it is important to point out that significant scientific and policy challenges face the EPA in the evaluation, interpretation, and application of the results coming from the testing of mixtures.~~

e?

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f?

~~Although some of these challenges are similar to those encountered with single chemicals, many of them are unique to mixtures, and particularly to those mixtures found in the environment.~~ The EDSTAC urges EPA to identify the ~~policy and scientific~~ challenges it faces early in this endeavor, and to~~and that the issues be~~ address these issue~~sed~~ in a transparent fashion. ~~Nonetheless, the EDSTAC urges EPA to rigorously address the science of mixture toxicology in the Agency's research efforts, and the Committee recognizes the need, under the auspices of the EDSTAC, to begin to confront mixtures.~~

g?

h? The recommendations that follow are based on the assumption that, prior to undertaking the T1S step of the program, the following will occur:

i?

1? Demonstration/Validation (D/V) of both HTPS and the T1S battery – a limited number of chemicals will be selected and evaluated in the battery of screens recommended by the EDSTAC. The purpose of this D/V phase is to show the utility and validity of the screens to be used in both HTPS and T1S.

a?

2? High Throughput Pre-Screening (HTPS) – a series of assays (receptor binding and transcriptional activation) will be selected for utilization in the high throughput mode.

a? Specific recommendations for mixtures:

a? 1. Demonstration/Validation – Include a limited set of mixtures in the D/V phase of screening, including those to be included in HTPS. For the purpose of this phase, a set of mixtures should be selected that spans a range of physical and chemical properties. The goal here is to challenge T1S and HTPS with a variety of chemicals to ensure feasibility and robustness *before* evaluating other mixtures. Clearly, the mixtures chosen for validation may be drawn from mixtures found in the environment and may include "known" endocrine disruptors, but the primary selection criterion should be chemical diversity. This component of the D/V phase is in addition to any D/V efforts done for individual chemicals, as described above.

b?

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c? 2. HTPS – If the screens are shown to be capable of handling single components as well as a diverse set of mixtures in the D/V phase, expert judgment (e.g., EDSTAC consensus), guided by a set of prioritization criteria, should be used to evaluate a limited sample of the literature and to decide on a limited set of mixtures to enter HTPS. Rather than focusing on chemical diversity as in the initial D/V phase, these mixtures should be representative of those found in environmental media or biological tissues. For each mixture, a set of chemicals should be identified that are deemed representative of the chemicals and their proportions found in the selected mixture. At the December plenary, the EDSTAC recommended that the PSWG develop selection criteria and identify a set of mixtures to enter HTPS. These criteria and the set of mixtures are described below in Section F.4.

d?

e? 3. Screening and Testing

a? a) The battery of screens validated for use in the screening program should be used to evaluate the mixtures examined in HTPS. If appropriate, screening should be followed by testing.

b?

c? b) A comprehensive literature evaluation should be undertaken to identify exposure and effects data on mixtures that have not already undergone HTPS. This information should be used to inform the prioritization for Phase II and subsequent phases. During the time it would take to accomplish this, data could be gathered from the screening and testing of single compounds during Phase I and from a limited number of mixtures to help inform the prioritization of other candidate mixtures. The prioritization of mixtures for Phase II and subsequent phases would use the same prioritization criteria as those used for single chemicals.

d?

e? 4)

Highest Priority Mixtures for Screening and Testing – The EDSTAC is concerned that the sheer complexity of the mixtures issue could produce “paralysis by analysis” and result in no meaningful forward progress. To overcome this inertia the EDSTAC urges EPA to begin work immediately on six mixtures, one drawn from each of six categories. By applying the effects and exposure criteria established for priority setting and outlined in Chapter Four, the following candidate categories of mixtures are recommended for early analysis. By no means does the EDSTAC underestimate the enormous challenge of addressing just these six, but a systematic approach to

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doing so could shed light on a wide range of technical challenges, help validate screens and tests, and promote development of decision-making protocols for screening and testing of mixtures. The Committee recommends that one representative mixture be selected from each of the following categories and be subjected to HTPS (if feasible), T1S, and, if necessary, T2T:

f?

g? a)

Contaminants in human breast milk -- The contaminants in human breast milk are recommended for immediate attention because infants are directly exposed to them. Existing literature demonstrates that human breast milk in the United States and elsewhere is contaminated with a sizable number of chemicals that tend to exist in common proportions. (See Allan A. Jensen and Stuart A. Slorach (eds.), Chemical Contaminants in Breast Milk (Boca Raton, FL: CRC Press, 1990)). Scientific opinion favors breast feeding over reliance on infant formulas and cows' milk in most cases. Therefore, the results of testing contaminants in human breast milk must be communicated with great sensitivity. The safety of breast feeding should not be considered diminished by the findings.

h?

The EDSTAC acknowledges that if hazards are recognized in breast milk, no techniques exist for reducing immediately the hazards to those exposed. But women have a right to know the extent to which they have been exposed to endocrine disrupting chemicals and are entitled to know the hazards to which they are subjecting their infants. Over the long term, the evidence from analysis of contaminants in breast milk can be an impetus to the evaluation of policies for reducing further exposure to such chemicals.

a?

b? b) Phytoestrogens in soy-based infant formulas -- Throughout this report, the EDSTAC has emphasized the comparative evaluation of synthetic chemicals and naturally occurring non-steroidal estrogenic substances (NONEs). Soy-based infant formulas contain a complex mixture of plant-derived NONEs – often referred to as "phytoestrogens." In particular, the formulas contain a category of phytoestrogens called isoflavones, specifically genistein and daidzein. But the formulas also contain a wide array of other isoflavones, present as minor components, which also possess estrogenic characteristics. Therefore, the EDSTAC recommends the screening and testing of the mixture of phytoestrogens in soy-based formula.

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c?

d? c) Mixtures of chemicals most commonly found at hazardous waste sites -- The Agency for Toxic Substances Disease Registry (ATSDR) has published a summary of the combinations of chemicals most commonly found at hazardous waste sites. (Barry L. Johnson and Christopher T. De Rosa, "Chemical Mixtures Released from Hazardous Waste Sites: Implications for Health Risk Assessment, *Toxicology* 105 (1995), 145-156). These mixtures pose a potential hazard to the communities in which these sites are located and, to the extent that such sites are located in lower-income areas, their presence raises issues of environmental justice. Such sites are distributed broadly across the United States.

e?

f? d) Pesticide/fertilizer mixtures -- Pesticides and fertilizers have commonly been detected in surface water and groundwater across the United States. The National Toxicology Program of the National Institute for Environmental Health Sciences (NIEHS) has conducted tests for traditional reproductive and developmental toxicological endpoints of the most commonly occurring mixtures in California and Iowa, two heavily agricultural states. (See, e.g., Jerrold J. Heindel *et al*., "Assessment of the Reproductive and Developmental Toxicity of Pesticide/Fertilizer Mixtures Based on Confirmed Pesticide Contamination in California and Iowa Groundwater," Environmental and Applied Toxicology 22,(1994), 605-621). Screening and testing these mixtures will provide an opportunity to compare results to the toxicological data already available.

g?

h?

i? e) Disinfection byproducts -- Some of the chemicals used for purifying drinking water supplies produce byproducts that, ironically, may themselves pose a hazard to human health. EPA currently is reviewing monitoring data on disinfection byproducts, with the objective of setting priorities for screening and testing. EPA is whittling down a list of several hundred such byproducts and anticipates, in the short run, NEIHS/NTP initiating testing on approximately ten of these chemicals for carcinogenicity, immunotoxicitiy, and reproductive effects. Based on whatever results are available from this review and testing, the EDSTAC recommends subjecting one representative mixture of the most commonly occurring disinfection byproducts to screening and possible testing for endocrine disruption.

j?

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k? f) Gasoline -- Gasoline is a complex mixture of volatile organic compounds to which large numbers of the population are exposed by inhalation. Dermal exposure can also occur in occupational settings. The EDSTAC recommends this mixture for screening and testing.

a?

VIII. Recommendation to Screen Naturally Occurring Non-Steroidal Estrogens

A. Background

a? Naturally occurring non-steroidal estrogens (NONEs) include natural products derived from plants (phytoestrogens) and fungi (mycotoxins). NONEs are less active than estradiol and diethylstilbestrol (DES) in *in vitro* and *in vivo* assays, but the ubiquitous presence of these compounds in foods indicate that NONEs cannot be ignored (*references to be inserted*). Moreover, the potential additive and antagonist effects of NONEs with other endogenous and exogenous hormonally active chemical substances are issues that warrant investigation. Significant research on NONEs is being conducted in the United States and other countries to better characterize the benefits and potential hazards (effects) of, as well as the levels of exposure to, these estrogenic compounds.

b?

c? NONEs are commonly perceived as safe, generally beneficial, and overall innocuous to humans. For example, the low incidence of breast cancer in women within Asia has been attributed to the beneficial effects of the phytoestrogen genistein. Genistein is a major component in soybeans, which comprise a large part of the Asian diet. Moreover, phytoestrogens are recommended as safer, natural alternatives to steroidal estrogens for hormone replacement therapy. However, over the last 40 years, adverse effects of naturally occurring non-steroidal estrogenic compounds have been well-documented in wildlife (range livestock) and laboratory animals. In humans, there are reports that phytoestrogens prolong the menstrual cycle and cause (weak) proliferation of reproductive epithelial cells.

d?

e? Exposure to NONEs through food sources can occur throughout one's lifetime (i.e., *in utero*, infancy, childhood, and adulthood), and the level of exposure may vastly exceed

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typical pesticide crop residues. For example, significant quantities of a complex mixture of isoflavone phytoestrogens (predominately genistein and daidzen) are present in various soy-based foods. Soybean infant formulas are widely used in the U.S. and abroad, and there is research under way to determine the effects of these compounds on male infants. Additionally, the exposure and uptake of NONEs in adults is evident because phytoestrogens have also been detected in human breast milk and urine.

f?

g? The potential effects of NONEs, beneficial and detrimental, should not be dismissed or assumed to be non-existent because of an "evolved" ability of organisms to metabolize these compounds. Many of the endocrine disruption issues and concerns for pesticides and industrial chemicals are equally relevant for NONEs. There is substantial evidence to justify a designation of high priority for screening and testing of these compounds based on the exposure to and potential effects of NONEs to both wildlife and human populations. While there is an abundant amount of *in vitro* and *in vivo* screening data (mainly uterotrophic and estrogen receptor binding assays) on NONEs, broad-based mechanistic screening and two-generation/developmental toxicity testing (according to current guideline standards for pesticides and chemicals) is lacking.

h?

i? A review of the literature indicates that:

1? Estrogenic plant and fungal natural products are ubiquitous in nature and occur in significant quantities in foods (at least 20 fruits and vegetables), beverages (coffee, beer, wine, and bourbon whiskey), and forage (clover) (*references to be inserted*).

2? NONE levels vastly exceed pesticide residues in food. The typical daily intake of isoflavones by humans, estimated to be 0.6 mg/kg/day, can prolong a human female's menstrual cycle. The daily intake of a vegetarian who consumes very large quantities of soy-derived nutrients could be much higher (*references to be inserted*).

3? Coumesterol is uterotrophic in female rats fed over a 90-hour period at levels within the range reported in human foods (*references to be inserted*).

4? The deleterious effects of clover phytoestrogens on grazing sheep are well documented. Effects range from temporary and permanent infertility to permanent abnormalities in the reproductive organs (*references to be inserted*).

5? At doses up to 50 mg/day by oral administration, zearalenone, a corn mycotoxin, produces effects on the vulva, uterus, ovary, cervix, and mammary glands of swine similar to those caused by intramuscular injection of up to two mg of estradiol cypionate (*references to be inserted*).

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6? Phytoestrogens (genistein) can be both tumor promoters and inhibitors depending on the target organ and the dose. Genistein has been observed to inhibit both tyrosine kinase and topoisomerase II. The latter is the target site of action for taxol, a drug currently used to treat breast cancer (*references to be inserted*).

7? NONEs may produce various biological responses *in vivo*. NONEs may act as estrogen agonists or antagonists (anti-estrogenic effects). These effects could either be beneficial or deleterious depending on the target tissue. Additionally, NONEs may cause other responses through other mechanisms that do not involve the estrogen receptor. For example, phytoestrogens may alter the concentration of sex-hormone-bonding globulin which, in turn, alters the bioavailability of endogenous hormones (*references to be inserted*).

B. Recommendation

The EDSTAC therefore recommends screening and, if necessary, testing: 1) representative NONEs singularly; and 2) a complex mixture of NONEs (e.g., soy-based infant formulas as discussed in Section VII of this chapter). Data from the representative compounds could serve as comparison benchmarks for synthetic chemicals. Representative compounds should come from the major chemical classes of estrogenic natural products. Testing soy-based infant formulas should be made part of the initial investigation to evaluate mixtures.

The following NONEs were chosen from the literature based on their reported effects (beneficial and deleterious) to wildlife and/or humans and on their widespread occurrence in nature. These NONEs should be screened and, if necessary, tested.

Representative NONEs:

i? Isoflavones: genistein, daidzein, miroestrol, biochanin A, formononetin, equol
ii? Flavanones: kaemferol, naringenin
iii? Coumestans: coumesterol
iv? Dihydrochalcones: phoretin
v? Triterpenes: Betulafolienetriol (ginseng)
vi? Lignans: Enterolactone

Representative estrogenic mycotoxin:

7. Beta-resorcyclic lactones: zearalenone, zearalenol

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IX.
Recommendation for a Nominations Process

A. Introduction

The EDSTAC recommends that EPA establish a process that would allow affected citizens to nominate chemical substances or mixtures (CSMs) for endocrine disruptor screening and testing. In general, the nominations process recommended by the EDSTAC is intended to focus on CSMs where exposures are disproportionately experienced by identifiable groups, communities, or ecosystems rather than on CSMs where exposures are more broadly experienced by the general population at the regional and/or national levels. As such, the nominations process is intended to provide a mechanism for prioritizing CSMs that are unlikely to be considered as high priority through the core priority setting process. For this reason, the EDSTAC recommends that the nominations process should run parallel to, but be separate and distinct from, the core priority setting process described earlier in this chapter.

B. Description of the Nominations Process

Consistent with the overall philosophy of the core priority setting process, as described in Section XI. of this chapter, chemical substances and mixtures that are nominated will, in effect, be placed in one of the "compartments" of the overall compartment-based approach to priority setting. The EDSTAC recommends that a goal for each phase of the EDSTP should be that no less than 5% ~~a set percentage, not to exceed~~ **[X #/%?]** of the total number of CSMs subjected to T1S, or a minimum of 10 CSMs should be drawn from substances receiving nominations but not selected through the main priority setting process. For each phase of the EDSTP, the nominated chemicals should be evaluated against the specialized criteria described below. Priorities for the nominated chemicals should be established in accordance with these specialized criteria on a separate track, rather than attempting to integrate the prioritization of the nominated chemicals with the chemicals that are selected for T1S through the core process. Any nominated CSM that becomes a priority for T1S through the core process should be removed from consideration within the list of nominated chemicals in order to ensure the priorities drawn from the nominations process will only compete against other nominated chemicals.

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The nominations process should allow for an early opportunity to submit nominations during each phase of the EDSTP. A call for nominations should be made via a public notice specifying both the criteria by which nominations will be evaluated and the deadline for submitting nominations. The time period for submitting nominations should end prior to the expected Federal Register (FR) notice announcing EPA's formal proposal for T1S priorities. As a part of the public comment period following such an announcement, members of the public should be given an opportunity to comment on all chemicals that are proposed for T1S. Chemicals not included in the priority list for each phase of the EDSTP could be nominated at the start of the next phase. However, the public comment period following the FR notice should not be considered a second opportunity to nominate chemicals for the current phase of the program.

C. Criteria for Evaluating Nominated Chemicals

As noted above, the EDSTAC recommends that the nominations process should utilize a different set of criteria than will be used for the core priority setting steps of the EDSTP, particularly with respect to exposure. The exposure-related criteria for the nominations process should be designed to allow for chemical substances and mixtures for which there may not be widespread exposures on a national scale, but for which there are exposures on a smaller scale, to be eligible to receive a priority status for T1S. Thus, the nominations process should focus on exposures that are disproportionately experienced by identifiable groups, communities, or ecosystems.

After exposure-related criteria have been considered in the evaluation of nominated CSMs, it is likely that effects-related information will need to be considered to help further set priorities among nominations. This is potentially problematic because there is likely to be a lack of effects-related information. In fact, the lack of effects data may be the very reason for public concern. That is, communities may be regularly exposed to a CSM that has not undergone meaningful toxicological evaluation. Nevertheless, if there are effects data, or if the CSM is chemically similar to another CSM for which effects data are available, the Committee recommends that EPA utilize those data as a secondary source of information to help set priorities among nominees.

In summary, when evaluating nominations, EPA should consider nominated CSMs that meet the following criteria to be a higher priority than those that do not meet these criteria:

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1? CSMs for which there is a likelihood of a regularly completed exposure pathway as compared to CSMs for which the exposure pathway is likely to be completed only rarely or occasionally;
2? CSMs that affect a high proportion of people within a given community or workplace; and
3? CSMs for which there may be direct or indirect (i.e., model derived) effects-related data regarding the endocrine disrupting potential of the nominated CSM.

a?

b?

c?

D. Submission of Nominations

a?

b? ~~Although m~~Members of the public should be encouraged to submit nominations with as much information as possible, but it should still be permissible to do so without data or evidence as it relates to the specialized criteria. Lack of such information should not preclude EPA from evaluating a nominated chemical on a level playing field with nominated chemicals for which data have been submitted. EPA should make use of all information available to the Agency, including ~~any~~ anecdotal information that may be submitted, as well as information that is gathered as part of the core priority setting process (e.g., information contained within the EDPSD recommended in Section X. of this chapter). Recognizing that the nominations process may be vulnerable to misuse for various reasons, and that misuse could significantly detract from its intended purpose, the EDSTAC recommends that the nomination's process be as transparent as possible and that EPA provide the list of nominations (submitters and supporting information) in appropriate publications, Federal Register Notice and/or the Internet.

c?

d? In order to assist EPA in its evaluation of nominated chemicals, the Committee recommends that nominations ~~members of the public~~ should include ~~provide~~ the following types of information ~~when nominating chemicals~~:

e?

1? the nominator should identify themselves and/or their affiliation (i.e., individual, community group, nongovernmental organization, industry, etc.)
2? how exposure to the nominated CSM may be disproportional~~te~~ly experienced by identifiable groups, communities, or ecosystems;
3? the reasons for the nomination (which may include both exposure- and effects-related concerns) and any information that provides a basis for those concerns; and
4? the degree of support for the nomination from the potentially affected communities and/or workplaces.

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~~The EDSTAC recommends that the nominations process be designed and implemented in a manner that accomplishes its intended purpose. However, the EDSTAC recognizes that the nominations process is vulnerable to misuse and recommends that, during implementation, EPA safeguard against its use for unintended purposes. In particular, the EDSTAC recognizes that the nominations process is vulnerable to misuse for a number of reasons, including, but not limited to, gaining competitive advantage in the marketplace, for harassment, or to achieve strategic objectives in legal matters such as disputes between employees and employers or in toxic tort litigation. In addition to constituting an abuse of the nominations process, such misuse would dilute the nominations submitted for appropriate reasons and would thereby undermine the intent of the program. The EDSTAC strongly recommends that EPA implement measures to safeguard the nominations process against such abuse.~~

E. Mixtures in the Context of the Nominations Process

The EDSTAC expects and welcomes nominations of chemical mixtures as well as individual chemical substances. However, as with the broader discussion of mixtures contained in Section VII. of this chapter, the EDSTAC recognizes that there are difficult technical and policy issues surrounding the issue of screening and testing mixtures. The EDSTAC is particularly concerned that EPA and other governmental agencies, in anticipation of the nominations process raising expectations for action, be prepared to take whatever steps may be appropriate to address potential public health and environmental impacts that are identified through the EDSTP. Similarly, the EDSTAC recommends that the communication and outreach effort that will accompany the nominations process should address the capabilities, as well as the limitations, which EPA and other governmental agencies are likely to face in any subsequent effort to the screening and testing stage of the process.

F. Ability to Track Nominations

As recommended in Chapter Six of this report, members of the public should be able to track and locate the progress of all chemicals in the EDSTP through a centralized, on-line database run by EPA. This on-line database will provide an opportunity, in addition to the Federal Register notice, for members of the public to determine the status of chemicals that may be of concern to them.

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X.
The Endocrine Disruptor Priority Setting Database

A.
Introduction

As described in other sections of this chapter, the PSWG began its work by describing exposure- and effects-related information categories and criteria to be used for sorting and prioritizing chemicals for endocrine disruptor screening and testing. The PSWG also identified and evaluated data sources associated with these categories and criteria. These data sources are listed in matrices contained in Appendix G.

After identifying these data sources, the PSWG grappled with how to use them to sort and prioritize chemicals for endocrine disruptor screening and testing. Over time it became clear that there was much value and utility in pulling together the relevant and useful data sources into a single relational database, which is referred to as the Endocrine Disruptor Priority Setting Database (EDPSD). The PSWG had contemplated developing and using the EDPSD to assist in the EDSTAC's deliberations and, in particular, to help the work group and the Committee understand the implications of alternative approaches to priority setting. After making significant progress on the prototype EDPSD, the PSWG and the EDSTAC came to realize that the tool could not be completed given time and resource constraints.

This section presents recommendations on the further development, utilization, and maintenance of the prototype EDPSD. The recommended approach to priority setting contained in Section XI. of this chapter builds upon the recommendations contained in this section.

B. Recommendation and Principles to Guide the Continued Development, Utilization, and Maintenance of the Prototype EDPSD

The EDSTAC recommends that EPA continue to develop and maintain the EDPSD as a tool that can be used to expeditiously sort and prioritize chemicals for endocrine disruptor screening and testing. The EDSTAC identified several principles that should guide EPA's use of the EDPSD, along with the process EPA should follow in conjunction with use of the EDPSD.

Most importantly, the EDPSD itself, as well as the process by which it is utilized, should be open and transparent. As described in more detail below, EPA should convene a multi-stakeholder group

prior to the completion of the tool. This group would serve to help ensure that the tool was developed and ultimately used according to the guidelines suggested by the EDSTAC. EPA and the multi-stakeholder group should develop ground rules to prevent the use of the EDPSD to confirm *a priori* assumptions regarding the priority for screening specific chemicals or as a means to hide or obfuscate the basis for priority setting decisions. Further, EPA should provide notice and opportunity to comment on the proposed database tool before it is used by the Agency. Among other things, this will allow an opportunity for additional chemical-specific data that might not otherwise be included in the identified data sources to be incorporated into the database tool.

C.
Description of the Prototype EDPSD

The prototype EDPSD is a relational database that (as of December 1997) contains records for approximately 87,000 chemicals with Chemical Abstracts Service Registry Numbers (CASRNs) from data sources related to the information categories and criteria described in Sections III. and IV. of this document. It was created using Molecular Design Limited (MDL) Information Systems' Integrated Scientific Information System (ISIS). The CASRNs of discrete organic chemicals, polymers, and inorganic chemicals from each data source were entered in a multi-field format. The number of chemical records in the EDPSD is determined by the cumulative number of chemical records contained in each data field.

The data fields included in the prototype EDPSD were used to develop a form that appears on the computer screen during operation of the EDPSD (Figure 4.1). When queried using particular scenarios (e.g. how many TRI chemicals produced between 10,000 and one million pounds appear in Great Lakes fish (GLC Fish) and also occur in the Agency for Toxic Substances and Disease Registry (ATSDR) database, etc.), the EDPSD provides the number of chemicals meeting the criteria used. Any number of scenarios can be developed depending upon user interests. The prototype EDPSD showed great promise in providing numbers of chemicals that displayed certain criteria, and also has potential to develop algorithms combining different criteria. However, early queries using different scenarios occasionally resulted in numbers that were known to be inaccurate. It was assumed that the inaccuracies were resolvable by adequately cross-referencing the different data fields and conducting appropriate QA/QC correction to the data included in the fields. However, the QA/QC exercise could not be completed in the tight time frames of the EDSTAC schedule. As such, final development, demonstration, and validation of the EDPSD was viewed as a high priority, post-EDSTAC task for EPA with multi-stakeholder involvement. A more detailed description of the EDPSD follows.

All data fields in the EDPSD (Figure 4.2, Tables 4.1 and 4.2) are linked by CASRNs, and there are no duplicate records for any chemical. For most discrete organic chemicals, chemical formulas, molecular weights, and Simplified Molecular Input Line Entry System (SMILES) notations and chemical structures were entered into the EDPSD.

There are two types of fields in the EDPSD – logical and numerical. Logical fields are binary in nature (i.e., +/-, yes/no, true/false, etc.). For example, a chemical either is present or absent in a particular data source that is included in the EDPSD. Numerical fields by contrast are quantitative. They provide an actual measured value or, alternatively, an estimated number associated with a particular data source or environmental fate parameter (e.g., an estimated hydrolysis half-life of two hours).

As a relational database, the EDPSD may be queried in a wide variety of ways to answer questions in minutes that would otherwise take hours, days, or weeks to answer. For example, the EDPSD can be used to rapidly estimate the numbers and types of chemicals in different data sources that meet different criteria (e.g., the number of chemicals with annual production/importation volumes greater than one million pounds per year and log octanol water partition coefficients (LogP) > 6 that are measured in Great Lakes fish and identified by California's Proposition 65 as reproductive toxicants).

In short, the EDPSD is a very powerful tool for exploring alternative approaches to the application of the criteria described in Sections III. and IV. in this document. As described more fully in Section X. G. of this chapter, the EDSTAC recommends that EPA and the multi-stakeholder group should make full use of the EDPSD in an effort to advise the Agency on its final decisions for priority setting for T1S. However, the EDSTAC recommends that EPA and the multi-stakeholder group not be limited to data that can easily be placed into a database format such as the EDPSD when providing advice and making final decisions on priorities for T1S (see Section X. E. of this chapter).

D. Preliminary Recommendation for Data Fields to Be Included in the EDPSD

As noted above, significant progress was made in developing the EDPSD, but the tool was not completed given the time period and resources available to the EDSTAC. During the course of its work, the PSWG spent time grappling with the question of what data sources should be considered for inclusion in the EDPSD. This section outlines some of the PSWG's preliminary conclusions, which should be a starting point for the recommended development and implementation of the EDPSD to be completed by EPA and the proposed multi-stakeholder group. The following data

sources should be included, but are not considered to comprise a final comprehensive list. Rather, they illustrate the kinds of data sources that might be included in the final version of the EDPSD. The data field examples (Figure 4.2, Tables 4.1 and 4.2) are categorized by type, and each data field example is further described in Appendix G.

Figure 4.2. Example of data fields arranged into a form as they might appear on a computer screen

CASRN	MW	Formula	Name
SMILES			

Exposure-Related Criteria:

Biological Sampling

Environmental Sampling

Invertebrates, Fish, and Wildlife	GLC Fish	ATSDR/PL

Release to the Environment

Chemical Production or Importation

< 10,000 lbs.	> 10,000 < million lbs.	> million < billion lbs.	> billion lbs.

Site-limited intermediates	Polymers	Inorganics

Fate and Transport

LogP	Hydrolysis half-life (d)	Atmospheric (OH radical) half-life (d)	HLC (atm/cum/mole)	VP (mm/Hg)	Water solubility (mg/l)	K_{OC}	BCF

Effects-Related Criteria:

Laboratory Studies

Predicted Biological Activity/Effect
Epidemiology/Field Studies

RTECS	TSCATS 8(e) HE RTOX	TSCATS 8(e) EE RTOX	Prop 65

Statutory-Related Criteria

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FQPA SDWA

Active Ingredients	Inert Ingredients

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Table 4.1. Existing files (and field type) in the Endocrine Disruptor Priority Setting Database

[NOTE TO READER: More information on the existing and proposed data fields recommended for inclusion in the EDPSD may be found in Appendix G of this report.]

Generic and Notation Files:

1. **Descriptive** (all textual) – CASRN, Chemical Name, Chemical Formula and SMILES

A.

1. **Quantitative** (numerical) – Molecular Weight

Exposure-Related Criteria Files:

Biological Sampling Data (logical) – NHATS*

Environmental, Occupational, Food, and Consumer Product Data (logical) – Great Lakes Fish, Invertebrates, Fish and Wildlife, ATSDR/PL

Environmental Release Data (logical) – Toxics Release Inventory*

Production/Importation Volume Data (logical) – Annual Production Volume categories* for Discrete Organic Chemicals (≤10,000 lbs.; >10,000 ≤ 1,000,000 lbs.; >1,000,000 ≤ 1,000,000,000 lbs.; > 1,000,000,000); Site-Limited Intermediates, Polymers, Inorganics

Fate and Transport Data and Models (all numerical) – Estimated LogP (based on QSARs); Hydrolysis Half-Life, Atmospheric Half-Life, Henry's Law Constant, Vapor Pressure, K_{OC}, Water Solubility and Bioconcentration Factor

Effects-Related Criteria Files:

Toxicology Laboratory Studies & Epidemiology and Field Studies and Databases (all logical) – RTECS, TSCATS 8(e), HE RTOX, EE RTOX, and Proposition 65

Predictive Biological Activity or Effects Models (numerical) – Hologram QSAR for Estrogen Receptor Binding

Statutory-Related Criteria Files:

FQPA (logical) – Pesticide Active Ingredients and Inerts*

SDWA (logical) – Contaminant Candidate List*

(*****) Indicates data files that are currently logical, but could be changed to numerical with appropriate quality control and analysis.

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Table 4.2. Examples of file types that could be placed in the Endocrine Disruptor Priority Setting Database

Exposure-Related Criteria Files:

Biological Sampling Data – NHANES, TEAM, NHEXAS (when available)

Environmental, Occupational, Food, and Consumer Product Data – Published data on measured concentrations of industrial chemicals, pesticide active ingredients and inerts in air, drinking water, ground water, surface water, sediment, and soil (e.g., ACGIH/TLV, FDA/GRAS, OSHA/PEL, FDA/PAFA)

Environmental Release Data (logical or numerical) – ATSDR/HSEES (logical numerical) , USGS Pesticide Monitoring Program

Production/Importation Volume Data (logical or numerical) – Non-CBI Individual Production Volumes for Industrial Chemicals, Discrete Organic Chemicals, Polymers and Inorganics, Pesticide Active Ingredients and Inerts

Fate and Transport Data and Models (all numerical) – Measured Data for LogP, Hydrolysis Half-Life, Atmospheric Half-Life, Henry's Law Constant, Vapor Pressure, K_{oc}, Water Solubility and Bioconcentration Factor, Estimated and Measured Biodegradation Rate Data

Effects-Related Criteria Files:

Laboratory Toxicology Studies & Epidemiology and Field Studies and Databases* (all logical) – RTECS, TSCATS 8(e), HE RTOX, EE RTOX, and Proposition 65

Predictive Biological Activity or Effects Models (numerical) – Hologram QSAR for Estrogen Receptor Binding

Statutory-Related Criteria Files:

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FQPA (logical) – Pesticide Active Ingredients and Inerts*

SDWA (logical) – Contaminant Candidate List*

(*****) Indicates data files that are currently logical, but could be changed to numerical with appropriate quality control and analysis.

E. Special Handling of Effects Data in the Context of the EDPSD

The proposed EDPSD is a relational database tool that the EDSTAC recommends be used to assist in prioritizing chemicals for endocrine disruptor screening and testing. The prototype EDPSD has purposely been designed to be user-friendly, transparent, and flexible. However, these very qualities make it difficult, if not impossible, to include information from the general scientific literature that is not organized into accessible numerical or logical databases. Though this represents a significant shortcoming, the EDSTAC believes the EDPSD is sufficiently versatile to justify its use. However, the EDPSD should not be used in isolation from other "tools," nor should it be used to perform functions that do not lend themselves to its design.

There are numerous data sources that provide toxicological, epidemiological, or field study data that may be useful in prioritizing chemicals for endocrine disruptor screening and testing. Although far from comprehensive, published studies can be identified through widely available scientific literature databases such as Medline, Toxline, and NIOSHTIC.

Substance-specific reports are also widely available that include summarized data reviewed by the authors. Such reports are prepared by various organizations and agencies such as IARC, NIOSH (Criteria Documents), ATSDR (Toxicologic Profiles), to name a few. Other sources of compiled data exist in the substance-specific rules and rule-making dockets of regulatory agencies such as OSHA, EPA, CPSC, or on-line data summaries such as the EPA IRIS system. Less-exhaustive reviews are also found in agency investigative reports such as the NIOSH Health Hazard Evaluation reports or ATSDR hazardous site evaluations. Research grant progress and final reports submitted to NIH, EPA, private foundations, etc., on the other hand, are not widely available. Lastly, some companies maintain published literature databases relevant to their products as well as epidemiological data on the health experience of their work force. Unfortunately, for any given substance, chemical, or mixture, collecting and assessing most of these data is extraordinarily time consuming and resource intensive.

For these reasons, the EDSTAC recommends that EPA make use of the potentially valuable information contained in the scientific literature in an efficient and cost-effective manner. In particular, EPA should make use of all of the data that is available to it in a step-wise fashion, starting first with data that lends itself for inclusion in the EDPSD. This will include data from databases such as RTECS and TSCATS, which are limited to positive findings from the literature. Other databases that contain abstracts of studies but are not limited to positive findings could be searched next for those chemicals that either have positive findings in RTECS or TSCATS or that

warrant further review due to the application of other effects-related information or criteria (e.g., positive HTPS or QSAR results). Finally, if necessary and helpful to the process of either making or justifying the basis for final priority setting decisions, EPA could review the literature available on a particular chemical.

F. Continued Development of the EDPSD

In order to complete data collection in anticipation of the use of the EDPSD, data from additional files need to be included in the database, and the relevance of those files to priority setting for endocrine disruptor screening and testing needs to be provided as part of the justification for their addition. All new chemicals from each additional file must include, at a minimum, CASRNs and molecular weights. All new discrete organic chemicals from each additional file must also include SMILES notations and chemical structures.

The EDSTAC recommends that EPA provide resources to complete the QA/QC investigations of files that are currently in the EDPSD. The EDSTAC further recommends that EPA provide resources to add new files to the EDPSD in stages. These files and stages for their addition could include:

1st stage: EPA's and others' databases that provide use data for industrial chemicals and pesticides; information from pesticide ecotoxicity, fate, and toxicity one-liners; chemicals that are non-food-use pesticide active ingredients and non-food-use other pesticide ingredients; chemicals on the Generally Regarded As Safe (GRAS) list; and chemicals in the Priority Assessment of Food Additives (PAFA) database.

2nd stage: Use data that was not readily available in databases; chemicals and concentrations of chemicals in National Health and Nutrition Examination Survey (NHANES), Total Exposure Assessment Methodology (TEAM), and ATSDR's Hazardous Substances Emergency Events Surveillance (HSEES) files; measured chemical fate data; and additional QSARs for endocrine disruptors.

3rd stage: Inclusion of HTPS data and improved QSARs.

The EDSTAC recognizes that the time and resources required to add new files will depend upon a number of factors, including: when pending files are received; the format of received files; the

determination of whether to use files as sources of numerical or logical data; conversion of logical files to numerical files; completion of QA/QC investigations of the files and data; and expediency of the input process.

G. Use by Multi-Stakeholder Group

The EPA should convene a multi-stakeholder group prior to the completion of the tool. This group would serve to ensure that the tool was developed and ultimately used according to the guidelines provided by the EDSTAC. This multi-stakeholder group should provide assistance to EPA in developing this tool, but EPA would ultimately be responsible for setting priorities for T1S based on this tool. ~~The assembled group should then use the tool to assist in an effort to provide advice to EPA as to what its final priorities should be for T1S in Phase I.~~ Presumably, the group would follow the approach to priority setting recommended in Section XI. of this chapter. Specifically, the group should make use of the EDPSD to understand the implications of its recommendations to EPA regarding the number and types of chemicals that should be included on the list of priority chemicals for T1S in Phase I of the program.

The EDSTAC recommends that the multi-stakeholder group convened for this purpose should be approximately half the size of the EDSTAC, but with the same degree of balance and diversity of interests. ~~EPA should use this group to get reactions to decisions EPA has made in further developing the EDPSD, and then to use the tool to assist EPA as it makes its final decisions for the priorities for T1S.~~Further, the EDSTAC recommends that the Agency propose for public comment the database tool. Among other things, this will allow an opportunity for submission of additional chemical-specific data to be incorporated into the database tool. The EDSTAC also recommends that, after receiving comment on the tool itself, EPA propose for public comment its T1S priorities.

EPA should establish ground rules for the multi-stakeholder group that encourage the group to stay focused on the development of a fair and scientifically sound set of final recommendations of priorities for T1S. The ground rules should encourage the assembled group not to use the EDPSD as a tool that simply confirms or justifies a set of *a priori* assumptions.

H. Maintenance

In order for the EDPSD to remain a timely and viable tool, the EDSTAC recommends that EPA update the database every six months at a minimum, and more frequently if time and resources

permit. If maintained properly, the EDSTAC believes the tool will not only provide the capability to understand the "real-world" implications of alternative approaches to priority setting, but the tool will also have broad application and pertinence, once knowledge of the existence of the tool spreads.

XI.
Recommended Approach to Priority Setting

A. Introduction

To remind the reader of the context within which the EDSTAC's recommended approach to priority setting will occur, please recall the EDSTAC recommendation to establish an initial sorting step to separate the universe of chemicals that need to be considered for endocrine disruptor screening and testing into four distinct categories:

polymers that will be placed into a "hold" status (with some exceptions) pending a review of their monomers and oligomers;
chemicals for which there is insufficient data to proceed to either Tier 2 Testing (T2T) or hazard assessment and will therefore need to be prioritized for Tier 1 Screening (T1S);
chemicals for which sufficient data exists to go to T2T; and
chemicals for which sufficient data exists to go to hazard assessment.

In this concluding section of the Priority Setting chapter, a number of issues are presented which the PSWG considered in developing its recommendations, followed by the EDSTAC's recommended approach to setting priorities for T1S. Also included is the EDSTAC's rationale for its recommendation to rely on EPA's schedule for tolerance reassessments under the FQPA as the basis for setting priorities for food-use pesticides that will be permitted to bypass T1S and go directly to T2T.

B. Obstacles to an Ideal Priority Setting System

In an ideal world, the EDSTAC would have sufficient information on exposures to and effects from candidate chemicals to provide a basis for priority setting. In reality, existing data sets

are uneven in quality and quantity. The EDSTAC's review of available data, contained in Sections III. and IV. and Appendix G, attests to these problems. Major characteristics of this unevenness include the following:

Many more data are available on the effects of the relatively small number of active ingredients in pesticides (circa 600) than on the thousands of industrial chemicals produced in much larger quantities.

Biological monitoring data for humans are scarce. A relatively small number of chemicals (on the order of 100 or less) have been routinely sampled in human blood and urine in the United States, and the major U.S. national program for sampling concentrations in human tissues was discontinued in 1990.

Monitoring data for other organisms, while more numerous than human data, still focus on a relatively small number of chemicals.

Data on routine chemical releases to the environment, while markedly better than they were prior to the creation of the Toxic Release Inventory about 10 years ago, still encompass only 528 industrial chemicals and frequently rely on engineering estimates rather than actual releases.

C. Principles for Setting Priorities

The EDSTAC's report could have been designed primarily to assist EPA in implementing screening provisions of the FQPA and the SDWA. But, as noted earlier, the EDSTAC saw its charge as reaching beyond these specific statutes and EPA's regulatory authority. The EDSTAC acknowledges that EPA's implementation of these priority setting recommendations will be influenced most heavily by its statutory authorities. Nevertheless, the EDSTAC hopes its broad, scientifically derived approach will encourage voluntary testing behavior within the private sector and new screening and testing initiatives by other agencies.

The proposed priority setting system for T1S is based on the following three principles:

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1.
The system should be "transparent."

Environmental health concerns in the United States usually are addressed in decisions that represent a mix of scientific judgment and individual and shared values. Priority setting for endocrine active chemicals is especially value-laden, because necessary knowledge of effects and exposures is so lacking. There are many different, reasonable, and not obviously wrong ways of deciding how to apply the information categories and criteria identified by the EDSTAC. The manner in which these are used should identify as clearly as possible the weights assigned to various categories and the rationales underlying those weights.

2. The system should reflect guiding principles derived from the EDSTAC's review of existing data on effects and exposures.

Sections III and IV of this chapter present the EDSTAC's major conclusions about the strengths and limitations of the information included in each exposure- and effects-related information category, and a set of guiding principles for how to use this information in setting priorities. These guiding principles are principles for weighting data. A nonexhaustive list includes, for example:

The greater the relevance of a biological sampling data set to large populations, disproportionately exposed subpopulations, or particularly susceptible subpopulations, the more weight the data set should be given.
The more likely a chemical is to be internalized by an organism from its environment, the greater weight it should be given.
The more likely environmental releases are to lead to organism exposure, the greater weight the release data should be given.

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Production volume should not be used to prioritize between existing industrial chemicals and pesticides, because production volumes for high-volume industrial chemicals are several orders of magnitude higher than those for pesticides.

3.

The system should rely heavily on empirical data, but the highest priority should not be assigned solely to those chemicals for which the most empirical information on exposures and effects has been gathered.~~be driven by empirical data, but not be captive to it.~~

~~The EDSTAC prefers relying on empirical rather than modeled evidence of exposures.~~ The most solid evidence of exposures comes from ~~the~~ monitoring of ~~living~~ organisms, including humans. However, the number of chemicals monitored in this fashion is limited. Chemicals detected~~found~~ in ~~living~~ organisms should be weighted heavily~~highly~~ in the priority setting system. Therefore, chemicals that may not be widely monitored in organisms or environmental media, yet are~~, but not to the exclusion of chemicals that, while not widely monitored, are~~ nevertheless of potential concern, should not be excluded completely from the highest priority rankings. Existing empirical data on selected chemicals can and should be used to improve the predictive capacity of models that might be used as appropriate in addressing other chemicals for which empirical data are lacking.~~The "lamp post science" problem alluded to in Section III. -- focusing exclusively on the chemicals about which the most is known -- must be avoided.~~

The EDSTAC also prefers weighting heavily~~relying on~~ empirical ~~rather than modeled~~ evidence of effects, at least until it is learned how to develop better models for use in the assessment process. The EDSTAC recognizes that there is a risk that heavily weighting ~~highly~~ those chemicals about which the most is known may penalize those chemical producers who have evaluated the potential effects of their products. The Committee acknowledges this possibility, but it should be kept in perspective. It applies mainly to active ingredients in pesticides. Since the food-use pesticides (circa 470 of circa 600 registered active ingredients) may go directly to T2T anyway, thereby skipping T1S, the availability of large amounts of data on these pesticides will not raise their priority for T1S higher.

D. Recommended Strategy for Setting Priorities for Tier 1 Screening

The EDSTAC advocates adoption of a "Compartment-Based Priority Setting Strategy." Such a strategy builds directly upon the several distinct exposure- and effects-related information categories and criteria found in Sections III and IV, respectively, as well as several specially targeted priorities identified elsewhere in this chapter, including: mixtures (Section VII), naturally occurring non-steroidal estrogens (Section VIII), and nominations (Section IX). The basic premise of a compartment-based priority setting strategy is to establish separate priorities for a limited number of separate compartments. The term "compartment" simply refers to the particular information category or criterion or combinations of information categories or criteria that define each set of priorities. Such compartments can be defined by the integration of exposure and effects data, the consideration of exposure data on its own, effects data on it own, or specially targeted priorities, as described below.

A compartment-based approach can be contrasted with approaches that strive to develop a single rank-ordered priority list that integrates all exposure- and effects-related information categories and criteria. Although the EDSTAC describes one such approach below, the Committee believes the proposed compartmentalized approach, best accommodates its principles for priority setting and the real-world situation of uneven data.

E. Illustrative Compartments for the Recommended Priority Setting Strategy

[NOTE TO THE READER: The EDSTAC endorses the general framework of a "compartment-based priority setting strategy," but the specific compartments and the weights and/or order in which they should be utilized have not yet been agreed upon. Thus, the compartments described immediately below are solely illustrations.]

Where the EDSTAC was confident of the data that are pertinent to a particular compartment, the number of chemicals estimated to fall within each compartment are indicated below. For some compartments, the EDSTAC did not have sufficient data to provide estimates. The compartments are NOT listed in order of agreed-upon priority.

As noted above, the illustrative compartments fall within four major categories:

Integrated exposure/effects -- Each of these compartments draws first from databases containing information on exposures. Within each compartment, priorities are set on the basis of effects data. *For purposes of illustration only*, these data on effects are presumed to come from TSCATS, RTECS, HTPS, and QSAR models. These are the databases currently projected for inclusion in the EDPSD. Elsewhere in this chapter, the challenge of readily assessing effects data, and the desirability of taking a "tiered approach" to such assessments that digs more deeply into or goes beyond data bases such as those mentioned specifically above are described. It is anticipated that most of the chemicals in Phase I will be prioritized based on integrated exposure and effects data.

Exposure Only -- Compartments in this category would prioritize chemicals based on exposure data only, without using effects data. It is anticipated that chemicals in these compartments would be relatively few compared to those taken from integrated compartments. These compartments would focus on identifying chemicals with high production volumes. ~~Any compartments under this category would be derived solely from exposure-related data, without regard to or integration with effects-related data.~~ (N. Kim, plenary)

Effects Only -- Compartments in this category would prioritize chemicals based on effects data only, without using exposure data. It is anticipated that chemicals prioritized in these compartments taken for screening in any one phase would be relatively few compared to those taken from integrated compartments. These compartments would focus on identifying chemicals with noteworthy effects data. ~~Any compartments under this category would be derived solely from effects-related data, without regard to or integration with exposure-related data.~~

Specially targeted categories -- These categories include mixtures, nominations, and non-steroidal estrogens. These presume widespread exposure and the possibility of widespread effects. The nominations category can include less widespread, yet elevated exposures and can be driven by reported effects that might be associated with exposures to chemicals.

1. <u>Illustrative Integrated Exposure/Effects Compartments</u>

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a)
Chemicals found in human biological samples

These are the most solid indicators of human exposure. They include chemicals from the NHATS, NHANES, and TEAM studies described earlier in this chapter and in Appendix G, Table 1, and number approximately 100 chemicals. Some of these substances may bypass T1S and go directly to T2T. Priorities for screening among the remaining substances can be established based on effects data, with the highest priority given to chemicals on this list for which there is some indication of possible biological effects. The EDSTAC acknowledges that some of the human sampling data are not current, but believes they nevertheless are worthwhile to use.

b)
Chemicals found in wildlife samples

These are the most solid indicators of wildlife exposure. U.S. Fish and Wildlife Service's Environmental Contaminant Data Management System lists 625 compounds and the Great Lakes Fish Monitoring Program lists over 550 compounds. (See Appendix G, Table 1.) Priorities among these chemicals can be set based on effects.

c)
Highest volume chemical releases from industrial sites

This component draws on the Toxic Release Inventory, which includes 528

chemicals. Priorities within the compartment would be based on evaluation of effects data.

d)
Commonly occurring chemicals at hazardous waste sites

ATSDR has published a list of the most commonly occurring chemicals at hazardous waste sites. (See Johnson and De Rosa, "Chemical Mixtures Released from Hazardous Waste Sites: Implications for Health Risk Assessment," *Toxicology* 105 (1995) 145-156.) These pose a potential hazard to the communities in which these sites are located and, to the extent that such sites are located in lower-income areas, the presence of these sites raises profound issues of environmental justice. These sites are distributed broadly across the United States. Priorities within this compartment would be based on evaluation in Environmental Fate and Transport models and assessment of pertinent effects data.

e)
Cosmetics, food additives, and related substances within FDA jurisdiction

This compartment includes substances like cosmetics and food additives which are eaten or are intended to be put on the skin of humans. Therefore, exposure is widespread. Priorities for screening within this compartment would be based on evaluation of data on effects, to the extent that such data are readily available.

f)
Chemicals to which there is widespread occupational exposure,

g)
Chemicals in products to which there is widespread consumer (especially child) exposure

2. Exposures Only

a)
High-production volume chemicals

A limited number of chemicals would be drawn from this compartment. These chemicals would have very high production or import volumes and would be included unless there were clear reasons to believe that exposures would not be likely (e.g., a chemical is site limited and not stable). This category would identify chemicals with high exposure potential that are unlikely to be selected in an exposure/effects integrated approach because of few or no effects data. (N. Kim, plenary)~~This compartment could include chemicals produced or imported in amounts greater than one billion pounds per year, as shown in the TSCA Inventory. This compartment numbers XXXX. Site-limited intermediates would be excluded. To further set priorities within this compartment, chemicals would be analyzed in environmental fate and transport models to estimate the likelihood of exposures to humans or other living organisms.~~

3. Effects Only

a)
Results of HTPS

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A relatively small number of chemicals are expected in this category. HTPS is designed to increase available knowledge on effects of chemicals, especially for those chemicals about which little is known. The results of HTPS can assist in setting priorities within other compartments, but can also be used on a "stand-alone" basis, as indicated above. Alternatively, this compartment could contain any chemicals that have a positive result in the HTPS assays, but are not otherwise identified as a priority under any of the compartments described above. Chemicals in this compartment could be ranked based on determination in HTPS regarding their potency, while acknowledging that HTPS does not address the full range of endocrine disrupting mechanisms.

b)
Results of Epidemiology Assessments

Case reports, environmental justice reports, retrospection studies, etc., may also provide effects data in the absence of (or with inadequate) exposure data; i.e., this compartment could contain chemicals that are not otherwise identified as priorities.

4. Specially Targeted Compartments

a) Mixtures

People and other living organisms are exposed continually to mixtures. The EDSTAC does not underestimate the difficulty of addressing these mixtures. Nevertheless, initial steps *must* be taken to understand the implications of these exposures. In Section VII., the EDSTAC identified six types of mixtures from

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which a total of six representative samples of mixtures (one from each type) should be selected as a priority for T1S. It is the Committee's belief that its recommendations represent a reasonable and prudent approach.

b)
Naturally occurring non-steroidal estrogens

As described in Section VIII., humans and other living organisms are broadly exposed to a wide range of naturally occurring chemicals that affect hormones. These substances are ubiquitous in food. Individuals exposed to them should be made aware of the benefits and hazards that may be associated with their consumption. Based on such information, consumers may be able to voluntarily alter their diets. As indicated in Section VIII., twelve such substances should be addressed in Phase I.

c)
Nominations

The EDSTAC recommends EPA establish a process to allow citizens to nominate chemicals for endocrine disruptor screening and testing. The purpose, criteria, and principles that should guide EPA in developing and implementing the recommended process are described in Section IX. of this chapter. ~~Establishing an open process for soliciting nominations and selecting the highest priorities will take some time. The Committee has arbitrarily suggested 50 nominated chemical substances as the target for Phase I, since it may not make sense to go to the trouble of funding a nominations process for a smaller number. The nominations process could be used to incorporate degradation byproducts of chemicals and site-limited mixtures not otherwise addressed by the priority setting scheme.~~ |

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F. Numbers of Chemicals Prioritized and Associated Weightings of Compartments

EPA has not provided the EDSTAC with a target for the number of chemicals the Agency believes should go through T1S in either Phase I, subsequent phases, or for the life of the program. The PSWG of the EDSTAC exchanged views about potential targets but did not attempted to reach consensus on this matter in the hopes of using the priority setting data base as a tool that could be used to explore alternative scenarios and targets.

Because the EDPSD was not completed before the drafting of the EDSTAC's final report, the EDSTAC (and, in particular, the PSWG that conducted this work on the EDSTAC's behalf) was unable to conduct a "reality check" on how the illustrative compartments might work in practice. It is hoped, however, that some scenarios will be run for at least some of the compartments before the EDSTAC's final report is submitted to EPA in mid-1998.

Thus, the number of chemicals to be selected for Tier 1 Screening is a major unknown in achieving greater specificity at this time on how the system should work in practice. For example, if only 100 chemicals can be screened in Phase 1, this dramatically reduces the number of chemicals that can be selected from each compartment, and may dictate the selection of a smaller number of compartments. On the other hand, if the number of chemicals to be screened is 1,500, this provides somewhat greater flexibility in selecting chemicals and could alter the weights assigned to different compartments.

To facilitate discussion of the compartment-based approach, *and for illustrative purposes only*, the Committee selected 1,500 as an upper estimate of the number of chemicals to be selected for the first phase of Tier 1 Screening. This number may strike some as too high and others as too low. It may exceed existing laboratory capacity, although it is assumed that laboratory capacity is not fixed and that the private sector testing market will respond to the demands imposed under EPA's new screening and testing requirements. The 1,500 figure is ambitious by historic screening and testing norms under TSCA, but is not so large as to be obviously unattainable. Finally, as noted previously, this figure excludes the 469 food-use pesticides that will go directly to T2T.

The 1,500 figure may appear low compared to the figure of 75,000+ chemicals in the TSCA Inventory, but this larger figure should be put in perspective. The Inventory includes many

chemicals that are no longer produced (although some of these, such as DDT and PCBs, either linger in the environment or remain in use); many polymers that are unlikely to be of concern from a perspective of endocrine disruption; many site-limited intermediate industrial chemicals; and many low-production volume chemicals that, because of how or where they are used, may not be worthy of attention for purposes of screening and testing.

Notwithstanding its size relative to the entire TSCA Inventory, the EDSTAC's upper boundary of screening 1,500 chemicals could encompass chemicals most widely found in biological samples, produced at highest volumes, released in greatest amounts and most likely to be of environmental concern, and several mixtures to which there is widespread exposure. Moreover, should a decision be made to raise the priority for screening of those chemicals that rank highest in multiple compartments, this will provide increased assurance that screening resources are being directed where they can be most helpful. Beyond these chemicals that rise to the top because of their high rankings in multiple compartments, the question of how many chemicals should be selected from each compartment is a heavily value-driven exercise. *For example and for illustrative purposes only*, one could take all or almost all of the chemicals from a compartment (e.g., measured concentrations in tissues and fluids of living organisms) that is deemed highly important relative to other compartments.

For example and for illustrative purposes only, 1,500 chemicals could be prioritized by:

Selecting 75% (1,125)~~800 (53%)~~ from the integrated exposure/effects compartments;
Selecting 10% (150)~~400 (27%)~~ from the exposure-only compartment(s);
Selecting 10% (150)~~200 (13%)~~ from the effects-only compartment(s); and
Selecting 5% (75)~~100 (7%)~~ from the specially targeted compartments.

The cost of screening 1,500 chemicals is estimated to range from $196~~20~~ million at the low end ~~(assuming the cost of the screening battery to be $80,000)~~ to $288~~180~~ million at the high end. This assumes the cost of a screening battery is $160,000 plus or minus 20%. These costs are uncertain, and will be distributed over several years. These estimates do not include the costs of the fish gonadal recrudescence assay and the frog metamorphosis assay. These two assays are in the research mode and their costs can only be estimated after they are standardized and validated. ~~(assuming the cost of the screening battery to be $120,000).~~ Screening and testing costs should be viewed in the context of the near- and long-term

benefits to society, including the considerable financial benefits of disease prevention and environmental protection. Such societal benefits are typically large, but difficult to quantify precisely.~~The estimated cost of a more modest program, e.g., EPA setting a target of 500 chemicals for screening during Phase 1, would be $40 million to $60 million. Out of consideration of laboratory capacity, cost, and other factors, EPA may decide it is most prudent to establish this more modest target. This reduced figure might change the distribution of chemicals selected from among the above four categories of compartments, and could change the number of chemicals selected from within individual compartments.~~

EPA could also set an extremely low target of 100 chemicals for T1S in Phase I of the EDSTP. The EDSTAC, however, believes such a goal would be setting sights too low.

G.
Next Steps (Reaching Closure) on Phase I Priorities for Screening and Testing

The EDSTAC believes it has created a strong, logical, transparent basis for setting priorities for T1S~~ier 1 Screening~~. ~~Building on the strong base described above, we believe we can refine the system further between mid-March and early June 1998, provided suitable progress is made in moving the priority setting database forward. But since there is a chance that closure will not be reached completely by that time, because of continuing limitations in the database, EDSTAC~~The Committee recommends that the multi-stakeholder group that is described in Section X. G. above use the EDPSD tool to experiment with the above categories and compartments to determine more finely the numbers of chemicals that emerge for T1S. The experiment can encompass including or excluding different quantitative thresholds for guiding decisions on the larger categories of priority chemicals, including parameters related to environmental fate and transport and parameters related to reported effects data.

Readers of this report should also be aware that EDSTAC's Priority Setting Work Group, which developed this chapter, also had placed before it by one of its members a "thought starter" on an approach very different from the compartment-based schema described above. The approach relies heavily on modeling data. It offers the potential of providing a three rank-ordered priority lists of chemicals, one for screening for each of the three hormonal systems addressed by the program–estrogen, androgen, and thyroid. The Priority Setting Work Group did not fully evaluate this alternative, but may do so by the March plenary for which this draft report is being prepared.

The sketched approach is inspired by work conducted at a "Pellston Workshop on Chemical Ranking and Scoring," conducted in February 1995 and published in Mary B. Swanson and Adam C. Socha (eds.), Chemical Ranking and Scoring: Guidelines for Relative Assessments of Chemicals (SETAC Press, 199X). Since that conference, the European Community has adopted EUSES, the European Uniform System for the Evaluation of Substances." It is used for risk assessment of both new and existing substances. The system contains models that can be used to estimate exposure concentrations or dose. The exposure models are for "global" exposure, and for environmental, workplace, and consumer exposure. They require chemical property data that are generally available or can be calculated using an estimation system such as EPA's SPARC. They also require production and use data. The production data are available, and arguably could be used as a rough surrogate in the absence of use data.

EUSES can calculate concentrations of chemicals in various media (including food), and these could be divided by HTPS values for effects to give a crude risk index. (Since HTPS produces separate results for E, A, and T effects, these separate results would have to be integrated in some fashion to produce a single rank-ordered priority list.) T1S for Phase I could start with the chemical that has the highest index and proceed down the list to the lowest. Because this approach rank-orders the priorities based on the HTPS data, it might be possible to stop screening compounds as one gets consistently negative T1S results at the lower end of the list.

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~~The approach described is markedly different from the compartment-based approach. It offers one integrated method of combining effects and exposure considerations, relying heavily on models and HTPS data. The compartment-based approach, in contrast, while it draws selectively on models (e.g., Environmental Fate and Transport models) and HTPS data, also draws heavily in some respects on what is known about actual exposures (as indicated by biological monitoring in humans and other organisms). The compartment-based approach also acknowledges that exposures and effects can be integrated in several different ways and that these several ways reflect differing values that deserve recognition in priority setting.~~

H. Recommended Approach to Setting Priorities for Tier 2 Testing During Phase I of the EDSTP

As described in Chapter Three, the EDSTAC is recommending that the owners/producers of chemicals should be permitted to bypass T1S under two alternative scenarios. "Scenario 1" covers chemicals for which two-generation toxicological studies are either required by statute (i.e., FIFRA) or where such studies have been completed in the past, but they did not include the additional T2T endocrine disruptor endpoints recommended by EDSTAC . "Scenario 2" covers chemicals where the owner/producer wishes to achieve the definitive results of T2T voluntarily without going through T1S.

This section focuses primarily on ~~addresses~~ the need to set priorities for the subset of Scenario 1, which includes food-use pesticides regulated under FIFRA/FQPA. As discussed below, the EDSTAC recommends that priorities for conducting T2T on food-use pesticides should be based on the FIFRA/FQPA re-registration and tolerance reassessment processes.

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Priority setting for T2T for chemicals other than food-use pesticides ~~The remaining subset of chemicals under Scenario 1 includes chemicals where~~ for which two-generation toxicity tests have been completed in the past but where the chemical is not regulated under FIFRA/FQPA~~. Priority setting for T2T for these chemicals~~, as well as chemicals that bypass T1S under "Scenario 2" ~~chemicals~~, will be driven by the actions of the owners/producers due to the inherently voluntary nature of the bypass of T1S that will occur with these chemicals.

Food-use chemicals that bypass T1S under Scenario 1 are likely to be the prime candidates for the alternative approaches to completing the information requirements for T2T described in Section VII. of Chapter Five. It is also assumed that it may be necessary to assess endocrine-mediated endpoints that had not been adequately assessed in past two-generation toxicity tests on these compounds. The determination of which alternative tests and/or additional endpoints will need to be conducted will be made on a case-specific basis.

~~In creating these "bypass options," t~~The EDSTAC recognizes it may be necessary to conduct a limited number of assays that are similar, if not identical, to those that would have been conducted during T1S for chemicals which are permitted to bypass the T1S battery. The purpose of conducting these assays as part of T2T is to gain knowledge about specific mechanisms of action that are necessary to complete the hazard assessment step~~.~~ and/or to determine whether any adverse effects observed in T2T are in fact endocrine mediated~~. It is also assumed that it will be necessary to assess endocrine-mediated endpoints that had not been adequately assessed in past two-generation toxicity tests on these compounds. Chemicals that bypass T1S under Scenario 1 are likely to be the prime candidates for the alternative approaches to completing the information requirements for T2T described in Section VII of Chapter Five. The determination of which assays or additional endpoints to be evaluated would be made on a case-specific basis.~~

~~Chemicals that meet this sorting criterion would be separated into food-use pesticides and all other chemicals. The priorities for conducting T2T on the chemicals other than food-use pesticides, including those chemicals for which the owner wishes to voluntarily bypass T1S, would be made on a case-specific basis. The priorities for conducting T2T on food-use pesticides would be based on the FIFRA/FQPA re-registration and tolerance reassessment processes.~~

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The decision to consider pesticides separately for priority setting was based on practical realities associated with scheduling in EPA's Office of Pesticide Programs. These include ongoing re-registration activities, which have been in progress for more than a decade, and new requirements for tolerance reassessment mandated under the Food Quality Protection Act. The two aforementioned issues represent the primary scheduling priorities in the Pesticides Program for the foreseeable future.

Under the re-registration program, EPA reviews older pesticides to ensure compliance with current scientific and regulatory policies. Re-registration is intended to update test data requirements and standards for approval which change over time. During re-registration the Agency issues Data Call-Ins (DCIs). The interval between issuance of the DCI and receipt of data is dependent upon the number and the kind of studies requested. Presently, re-registration is being conducted on compounds for which DCIs were issued en masse shortly after passage of the 1988 amendments to FIFRA or on a case-specific basis thereafter. For the most part, these data have been received by the Agency. Data were requested for 436 active ingredients, and Registration Eligibility Decisions (REDs) have been issued for 171 of the 436 pesticide ingredients. Generally, neither the DCIs nor REDs issued to date have systematically dealt with endocrine endpoints.

In addition to the re-registration process, food-use pesticides represent a category of pesticides for which EPA has already undertaken a hazard-based priority setting exercise. Then food-use pesticides are being reviewed with an eye to tightening regulatory treatment in light of new scientific data and statutory requirements. This priority setting exercise was mandated by Congress under Section 408(q)(3) of the FQPA. EPA is required to reassess tolerances for pesticide residues in or on raw and processed foods for both active and inert ingredients. EPA is directed to give priority review to pesticides that appear to present risk concerns based on existing data. In reassessing tolerances, EPA must consider:

aggregate exposure to the pesticide;
cumulative effects from other pesticides with a common mode of toxicity;
whether there is an increased susceptibility of exposure to the pesticide for infants and children; and
whether the pesticide produces an effect in humans similar to an effect produced by a naturally occurring estrogen and other endocrine effects.

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The FQPA requires EPA to review within 10 years all tolerances and exemptions established prior to FQPA's enactment on August 3, 1996. EPA is required to review 33% of applicable tolerances and exemptions by August 1999, 66% by August 2002, and 100% by August 2006. FQPA also required EPA to publish its review schedule within one year of the law's enactment, which EPA did on August 4, 1997 (62 Fed. Reg. 42019-42030). This general schedule developed by EPA for tolerance reassessment, along with re-registration, are the primary driving forces in scheduling regulatory actions for pesticides and their formulations and inert ingredients. With respect to tolerance reassessment, EPA has divided the pesticide reevaluation process into three categories, which will be reviewed in chronological order over 10 years:

Group 1, the highest priority class, includes organophosphate, carbamate, and organochlorine pesticides. It also includes pesticides classified by EPA as probable human carcinogens (groups B1 and B2 in EPA's carcinogen ranking system), and possible human carcinogens for which EPA has quantified a cancer potency (group C in EPA's carcinogen ranking system). Group 1 also includes high-hazard inert ingredients and any pesticides that appear to exceed their reference dose (RfD). Note RfD is defined as the daily exposure level of a pesticide, which, during the entire 70-year human lifetime, appears to be without appreciable risk on the basis of all of the facts known at the time. It is expressed in milligrams of the pesticides as it appears in the diet, per kilogram of body weight per day (mg/kg/bw/day). The RfD must not exceed 100%. The inclusion of certain pesticides in Group 1 is also driven by EPA's need to complete their re-registration by 2002, even though their tolerances may not appear to pose the greatest risk to public health. Also in Group 1 are pesticides for which tolerances and exemptions are in the process of being proposed for revocation.

Group 2 includes possible human carcinogens not included in Group 1. Others in Group 2 include remaining pesticides for which re-registration must be completed by 2002, and other pesticides included for other scheduling reasons.

Group 3 includes biological pesticides, those inert ingredients not identified as high hazard, and selected other pesticides. It should be noted that biopesticides, mainly the pathogenic microorganisms, are not amenable to endocrine disruption screening and testing.

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At the time of the FQPA's enactment, there were 9,728 tolerances and exemptions for active and formulation inert ingredients subject to the reassessment requirement. According to the EPA, 8,190 of these are tolerances for active ingredients, 712 are exemptions for active ingredients, and 826 are exemptions for inert ingredients. The total number of all active pesticide ingredients and inerts currently registered by EPA is approximately 1,800. This includes approximately 600 active ingredients and approximately 1,200 inerts. (Some of the inerts are also listed in the TSCA Inventory.) Of these 1,800, 469 are scheduled to be addressed through the tolerance reassessment process. This includes 228 in Group 1 (scheduled for review by August 1999), 93 in Group 2 (scheduled for review by August 2002), and 148 in Group 3 (scheduled for review by August 2006). There are an additional 823 inert ingredient exemptions that will be dealt with as part of Group 3.

There are both advantages and limitations to using the re-registration and tolerance reassessment processes as the basis for setting priorities for endocrine disruption screening and testing:

Re-registration and tolerance reassessment priorities were not established with endocrine disruption endpoints in mind. The current database of reproduction and developmental toxicity for most food-use pesticides reflects the 1988 guideline standards. Non-food-use pesticides may or may not have reproductive or developmental toxicity data depending on their specific use.

The priority setting process for food-use pesticides is driven by human health considerations, so the entire set of non-human, ecosystem-protection concerns of EDSTAC is not explicitly incorporated. However, most of the food-use pesticides with ecological concerns to off-target organisms appear on the Group 1 and Group 2 lists.

Notwithstanding these disadvantages, the EDSTAC recommends that the priorities EPA has established for the re-registration and tolerance reassessment process be used as the basis for the priorities for subjecting food-use pesticides to T2T. EPA's priority scheme for tolerance reassessment and exemption reviews encompasses many pesticides of potential concern for endocrine disruption, however, it leaves out several hundred non-food-use active and inert ingredients. These will be addressed using the recommended process for setting priorities for T1S as described above.

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