Chapter Seven

Compilation of EDSTAC Recommendations

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I. Chapter Overview

The following chapter provides a summary of the recommendations agreed to, in Chapters Three, Four, Five, and Six, by the EDSTAC regarding establishment of an endocrine disruptor screening and testing program. For more information regarding these recommendations, please see the respective chapters within this report.

II. Recommendations: Chapter Three – Conceptual Framework and Principles

1. The EDSTAC developed a tiered Conceptual Framework that formed the basis for its screening and testing strategy and all subsequent recommendations. The tiered framework consists of the following three major activities:

- **Priority setting** includes the sorting and prioritization of chemical substances and mixtures based on existing information. The existing information would be used to sort chemicals into four categories. An evaluation and analysis of this information will lead to sorting chemicals into one of four categories:

    - Polymers, which are placed into a "hold" status (with some exceptions) pending a review of their monomers and oligomers.
    - Chemicals for which there is insufficient data regarding endocrine disruption and will therefore need to be prioritized for Tier 1 Screening.
    - Chemicals for which sufficient data exists to proceed to Tier 2 Testing.
    - Chemicals for which sufficient data exists to go to hazard assessment.

- **Tier 1 Screening (T1S)** to detect chemical substances and mixtures capable of acting on endocrine systems.

- **Tier 2 Testing (T2T)** to determine, characterize, and quantify the nature of the endocrine disrupting properties of the chemical substances and mixtures identified by prior information and/or T1S.

2. The EDSTAC recommended the adoption of several principles to guide the use of the Conceptual Framework.

    - A chemical may bypass one or more tiers when warranted by appropriate information (e.g., sufficient prioritization data on endocrine disrupting properties to initiate T2T or

hazard assessment).
- If information is inadequate to determine if a chemical should move to the next tier, an active process should be developed for generating the needed information to make such a decision.
- Criteria and default assumptions for deciding whether chemicals move from one tier to the next should be developed in advance of initiating screening and testing.

3. Within the context of the Conceptual Framework, the EDSTAC recommends that the overall scope of the screening and testing strategy should:

   - be relevant to both human health and ecological effects;
   - initially emphasize identifying and characterizing effects that enhance, mimic, or inhibit estrogenic, androgenic, and thyroid hormone-related processes;
   - consider tests that detect multiple hormone interactions, address endpoints in multiple species, and predict long-term or delayed effects;
   - be periodically revisited to permit inclusion of additional hormone-mediated effects or new screens and tests as they become available;
   - be capable of evaluating the endocrine disrupting properties of chemical substances and common mixtures; and
   - allow determination of possible additive, synergistic, or antagonistic effects caused by interactions among the components of mixtures.

4. The EDSTAC recommends nine broad principles to guide the implementation of the endocrine disruptor screening and testing program. The screening and testing program should:

   - require the minimal number of screens and tests necessary to make sound decisions, thereby reducing the time needed to make these decisions;
   - examine existing screens and tests for their potential to predict, detect, and/or characterize endocrine disruptors, ensuring that any modification to existing screens and tests does not compromise their ability to predict other toxicity endpoints;
   - systematically examine existing screening and testing data not only for adverse endpoints in high dose groups, but also for physiological changes in low dose groups;
   - not detract from current and new efforts to assess the toxicity of compounds and mixtures through mechanisms other than endocrine disruption;
   - provide data that can be used for a broad range of management and regulatory programs in a form that supports international harmonization of their use;
   - include periodic review of new scientific information;
   - use a performance-based approach to the selection of screens, tests, and species, including the use of more appropriate screens, tests, and species as they are developed and validated;
   - be dynamic in order to stay current with the rapidly evolving science related to the

endocrine system; and
- be conducted at the minimum cost necessary to make the decisions within the EDSTAC Conceptual Framework.

5. The EDSTAC also recommended six guiding principles specific to the screens and tests themselves.

   - To facilitate making decisions within the EDSTAC Conceptual Framework, all screens and tests should have well-defined endpoints.
   - The use of animals should be reduced to the minimum level needed to obtain scientifically valid results and interpretations.
   - The results of screens and tests should support further research on effects of endocrine disruptors on populations, communities, and ecosystems.
   - In interpreting screening and testing results, a "weight-of-evidence" approach should be used, but should be consistent with a principle of prudence in protecting human health and the environment. In the case of T1S, this means that the strategy will err on the side of false positive identifications rather than false negatives.
   - Screening and testing results should be reported in a format that facilitates database development and analysis by a broad array of scientific, regulatory, and management organizations.
   - Decision criteria, such as those for determining statistical significance (e.g., necessary confidence intervals) and biological plausibility, should be clearly defined.

6. The EDSTAC recommends that T1S provide the minimum, yet valid and reliable, data to detect interactions with the endocrine system. In contrast to Tier 2 tests, T1S assays should:

   - be inexpensive, quick, and easy to perform;
   - be validated and standardized as soon as possible, defining characteristics such as sensitivity and specificity against a "gold standard," once it is identified;
   - be more "sensitive" than they are "specific," meaning that they should have as their primary objective the minimization of false negative or (Type II) errors, while permitting an as-of-yet undetermined, but acceptable, level of false positive or (Type I) errors;
   - capture multiple endpoints and reflect as many modes of endocrine action as possible;
   - be broadly predictive across species, gender, and age; and
   - yield data capable of being interpreted as either positive or negative for the purpose of determining whether and how to conduct T2T.

7. The EDSTAC recommends that T1S be used to make initial judgments about areas of concern in order to direct the focus of T2T. The interpretation of T1S results should be consistent with best scientific judgment, formed on the basis of considerations such as "weight-of-evidence," consistency of the data set, and methodological strengths and limitations.

8. The EDSTAC recommends that T2T be based upon T1S results and other relevant information. An underlying principle of T2T is that it should provide information useful for human and ecological hazard assessment. The T2T scheme should be flexible enough to allow for scientific judgment in the selection of the most appropriate tests and endpoints, and costs should be reasonable. Tests should be aimed at determining whether the chemical substance or mixture is an endocrine disruptor and whether the effects are a result of primary or secondary disturbances of endocrine function. In addition, these tests should be designed to establish the relationship between different exposure levels, timing and duration of exposure, and adverse effects, including developmental and reproductive effects on the individual and its progeny.

9. In contrast to T1S, the EDSTAC recommends that T2T should be both sensitive and specific, and designed to minimize false positive (Type I) and false negative (Type II) errors. Additionally, this battery of tests should:

    - include assessment of endpoints identified as relevant from Tier 1 screens;
    - include parental/offspring developmental endpoints (e.g., two-generation studies) in order to adequately evaluate all life stages;
    - include the life cycle of both viviparous (live birth) and oviparous (egg-laying) organisms;
    - be conducted at a range of doses that allow full characterization of the adverse effects of the chemical substance or mixture being tested;
    - be conducted in accordance with Good Laboratory Practice (GLP) regulations to the degree consistent with resources and the goal of timely decisions; and
    - be validated, if need be, as soon as possible against a clearly defined standard.

10. The EDSTAC recommends that a subset of the T1S *in vitro* assays be conducted with the assistance of automated technology to provide biological effects information to assist in the overall sorting and priority setting process. Because of the role this technology will play in the overall EDSTP, the EDSTAC refers to it as “high throughput pre-screening” (HTPS). The EDSTAC recommends that all chemicals currently produced in an amount equal to or greater than 10,000 pounds per year (estimated to be about 15,000 chemicals) be subjected to HTPS. Also, it is expected that *all* pesticides (i.e., both active ingredients and formulation inerts) will be subjected to HTPS. Any chemicals subjected to the assays conducted in the HTPS step would not be required to repeat the ER binding/transcriptional activation assay and the AR binding/transcriptional activation assay as part of T1S. On the other hand, for any chemicals not subjected to HTPS (e.g., production volumes less than 10,000 pounds per year), the assays in T1S would result in information equivalent to that which would have been provided from HTPS.

11. The EDSTAC recommends that the vast majority of chemicals go through priority setting, T1S, and T2T in a sequential manner. However, the EDSTAC also recognizes there may be individual cases in which T1S is bypassed. Three situations were identified where a chemical may bypass T1S, each with different implications for information requirements in T2T.

- Alternative means to meet T1S information requirements through the generation of data which are "functionally equivalent" to data derived from the recommended screening battery.
- Bypassing T1S for chemicals (e.g., food-use pesticides) that have previously been subjected to two-generation reproductive toxicity tests. Such chemicals should still be subjected to high throughput pre-screening assays.
- Bypassing T1S for chemicals for which there is no prior toxicology testing but the owner has voluntarily decided to proceed directly to testing. Such chemicals must be evaluated in the high throughput pre-screening assays, and all of the tests in the T2T battery.

III. Recommendations: Chapter Four – Priority Setting

A. Summary and Scope of Effort

The Priority Setting Work Group based its deliberations on the original Conceptual Framework described in Chapter Three. The work of the group revolved around adapting the Conceptual Framework and included the operational elements necessary for sorting and prioritizing chemicals. The core priority setting process that emerged contained several elements:

- the use of all available existing information;
- the development of a relational database to efficiently access and utilize information;
- an initial sorting of the universe of chemicals into categories based on an operationalized Conceptual Framework;
- the development of high throughput pre-screening data and its incorporation into the database;
- the use of the database to summarize empirical data and estimate fate and effect parameters where possible;
- the use of the database to establish criteria for sorting chemicals where appropriate; and
- the use of a compartment-based concept to accommodate subjective weighting where appropriate.

The EDSTAC viewed its role within EPA's broader mandate to protect human health and the environment and the broader testing authorities available to EPA. As such, the EDSTAC did not limit itself solely to requirements of the Food Quality Protection Act and the Safe Drinking Water Act Amendments of 1996. The Committee believes it is important to have priorities driven by scientific considerations and explicit value judgments, rather than by existing regulatory requirements.

B. The Universe of Chemicals and Initial Sorting

1. The EDSTAC recommends that pesticides, commodity chemicals, environmental contaminants, naturally occurring non-steroidal estrogens (e.g., phytoestrogens, mycotoxins), food additives, cosmetics, nutritional supplements, and a set of representative mixtures be prioritized for endocrine disruptor screening and testing.

2. The EDSTAC recommends that scientific considerations be used as the primary basis for prioritizing chemicals for endocrine disruptor screening and testing. Statutory authority to protect human health and the environment is embedded in long-standing federal legislation, as well as the Food Quality Protection Act and the Safe Drinking Water Act.

3. The EDSTAC recommends that the chemicals under consideration (approximately 87,000 compounds) be sorted into the following four primary categories based on the operationalized Conceptual Framework:

    - Polymers are to be placed on hold (with some exceptions) pending review of their monomers, oligomers, other components, additives, and degradation products (approximately 20,000 to 25,000 compounds).
    - Chemicals to be considered for endocrine disruptor screening (approximately 62,000 compounds) which lack sufficient data to be placed on hold or to proceed to definitive testing or hazard assessment will be subjected to the priority setting process for T1S.
    - Chemicals with sufficient data are to bypass screening and proceed directly to testing or hazard assessment (approximately 500 to 600 compounds).
    - Chemicals with sufficient data are to go to hazard assessment (expected to number approximately 50 to 100 compounds)

C. Polymers

4. With some exceptions, the EDSTAC concluded that, due to molecular weight, polymers are less cause for concern than other classes of chemicals with regard to endocrine disruption. However, there is some concern regarding the intestinal absorption capacity of neonates. Because of the lack of information on polymers produced prior to 1979 (the date of the initial TSCA Inventory), coupled with the low likelihood that polymers themselves are a concern for endocrine disruption, the EDSTAC offers the following recommendations.

    - All new polymers with a number average molecular weight (NAMW) greater than 1,000 daltons and all previously manufactured (or "existing") polymers (regardless of NAMW) are to be held from priority setting for endocrine disruptor screening and testing pending the outcome of the screening and testing of their monomer, oligomer, and other components.
    - The monomers, oligomers, and other components of polymers, as well as "new" polymers (i.e., those that went into production after 1979) with a NAMW less than 1,000 daltons

are to undergo priority setting, screening, and testing as appropriate.

- Chemicals on the EPA SDWA Contaminant Candidate List (CCL) should be used to identify the potential degradates of polymers which are most likely to present environmental exposure and which should, therefore, be subjected to priority setting, screening, and testing, as appropriate.

- If monomers, oligomers, or other components of a polymer are determined to have endocrine disrupting properties, an exposure assessment should be performed. 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 the Agency gains experience with endocrine disruptor screening and testing of monomers, oligomers, and "new" polymers (i.e., those that went into production after 1979) with NAMW less than 1,000 daltons, it should apply that experience toward development of an approach to address "existing" polymers (i.e., those that went into production before 1979).

D. Priority Setting Information Categories and Criteria

5. The EDSTAC recommends using existing exposure-related and effects-related data and information to establish criteria for accomplishing initial sorting. The Committee identified the following subcategories of information that could be used as the basis for sorting and priority setting and developed principles regarding their use.

Exposure-Related Information and Criteria

a) Biological sampling data
b) Environmental, occupational, consumer product, and food-related data
c) Environmental releases
d) Production volume
e) Fate and transport data and models

Effects-Related Information and Criteria

a) Toxicological laboratory studies and databases
b) Epidemiological and field studies and databases
c) Predictive biological activity or effects models (e.g., SARs, QSARs)
d) Results of high throughput pre-screening

E. High Throughput Pre-Screening

6. The EDSTAC found there was a general lack of endocrine effects data for the vast majority of chemicals. To address this problem, the EDSTAC recommends that, if demonstrated to be feasible, eight *in vitro* transcriptional activation assays should be conducted in a high throughput pre-screening mode (i.e., with the use of robotics and other automated processes). The objectives for conducting these assays in a high throughput mode is to:

- provide some information about the affinity of chemicals to bind to the estrogen, androgen, and/or thyroid hormone receptors;
- use this information in conjunction with other exposure- and effects-related information to determine the priority by which chemicals should be advanced to T1S;
- improve QSAR models;
- provide a source of information to help focus the selection of Tier 2 tests for those chemicals that bypass T1S; and
- generate data that can be used to identify chemicals that may be of concern at low doses.

7. The EDSTAC recommends that the high throughput pre-screening (HTPS) transcriptional activation assays be conducted on:

   - the estimated 15,000 chemicals that are currently produced in an amount equal to or greater than 10,000 pounds per year;
   - chemicals that are permitted to bypass T1S and go directly to T2T;
   - chemicals that are permitted to bypass both T1S and T2T and go directly to hazard assessment; and
   - all pesticides (both active ingredients and formulation inerts).

8. The EDSTAC recommends that HTPS results for the "bypass" chemicals not be used to set priorities for T1S, but to improve QSARs and inform dosing considerations, particularly during the interim period when research on low dose is being conducted, and to inform decisions regarding the types of tests that would need to be conducted in T2T.

9. The EDSTAC recommends that existing QSAR models be derived and supplemented with data from the HTPS assays, thereby expanding the predictive ability of these models.

10. The EDSTAC recommends that EPA explore the feasibility of creating an archive of a subset of HTPS project chemicals which can be accessed by researchers interested in studying endocrine mediated toxicity or in validating new screens for endocrine disruptors.

F. Mixtures

11. The EDSTAC recommends that EPA include a limited set of mixtures that span a range of physical and chemical properties in both the feasibility demonstration project for the HTPS assays, as well as the validation effort for the T1S assays.

12. If the screens are shown to be capable of handling a diverse set of mixtures in the HTPS feasibility demonstration project and the T1S validation steps, EPA should use expert judgment, guided by a set of prioritization criteria, to evaluate the literature and to decide on a limited set of mixtures to enter HTPS.

13. 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.

14. The EDSTAC recommends that a comprehensive literature evaluation be undertaken to identify exposure and effects data on mixtures that do not undergo HTPS. This information would be used to inform the prioritization for Phase II and subsequent phases of the screening and testing program which would use the same prioritization criteria as those used for single chemicals.

15. The EDSTAC recommends that representative sample mixtures be selected from the following categories and be subjected to HTPS (if feasible) and to T1S:

- contaminants in human breast milk;
- phytoestrogens in soy-based infant formulas;
- mixtures of chemicals most commonly found at hazardous waste sites;
- pesticide/Fertilizer mixtures;
- disinfection byproducts; and
- gasoline.

G. Naturally Occurring Non-Steroidal Estrogens (NONEs)

16. Naturally occurring non-steroidal estrogens include natural products derived by plants (phytoestrogens) and fungi (mycotoxins). Due to the ubiquitous presence of these compounds in foods, and due to the potential additive and antagonist effects of NONEs with other endogenous and exogenous hormonally active chemical substances, the EDSTAC recommends that:

- NONEs be included in the endocrine disruptor screening and testing program singly and in complex mixtures; and
- the following NONEs be screened and, if necessary, tested.

Representative NONEs:

- Isoflavones: genistein, daidzein, miroestrol, biochanin A, formononetin, equol
- Flavones: kaemferol, naringenin
- Coumestans: coumesterol
- Dihydrochalcones: phoretin
- Triterpenes: betulafolienetriol (ginseng)
- Lignans: enterolactone

Representative estrogenic mycotoxins:

- Beta-resorcyclic lactones: zearalenone, zearalenol, zearanol

H. Nominations

17. The core priority setting process recommended by the EDSTAC focuses on giving high priority to chemicals with widespread exposure at the national level. The EDSTAC recognizes such a process could result in a low priority for chemicals where exposures are disproportionately experienced by identifiable groups, communities, or ecosystems. Therefore, the EDSTAC recommends that EPA establish a nominations process that:

    - runs parallel to, but is separate and distinct from, the core priority setting process;
    - is designed to allow 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 for T1S;
    - allows for an early opportunity to submit nominations during each phase of the Endocrine Disruptor Screening and Testing Program; and
    - draws no less than 5% of the total number of chemical substances or mixtures subjected to T1S from substances receiving nominations but not selected through the main priority setting process.

18. The EDSTAC recommends that any nominated chemical substances and/or mixtures that becomes a priority for T1S through the core priority setting process be removed from consideration within the list of nominated chemicals in order to ensure that the priorities drawn from the nominations process will compete only against other nominated chemicals.

19. In keeping with the overall purpose of the nominations process, the EDSTAC recommends that a different set of exposure-related criteria be used to evaluate the priority for nominated chemicals compared to the exposure-related criteria that will be used for the core priority setting process. Specifically, the nominations process should focus on exposures that are disproportionately experienced by identifiable groups, communities, or ecosystems rather than focusing on chemicals for which there is widespread exposure in the aggregate.

20. The EDSTAC recommends that if there are effects data for the nominated chemical, or if the chemical is similar to another chemical substance or mixture for which effects data are available, EPA should utilize those data as a secondary source of information to help set priorities among nominees.

21. The EDSTAC recommends that when the relative priorities of nominated chemical substances or mixtures are evaluated, EPA should consider those that meet the following

criteria to be a higher priority than those that do not:

- chemical substances or mixtures where there is a likelihood of regular exposure, in contrast to those for which exposure occurs only rarely or occasionally;

- chemical substances or mixtures that affect a high proportion of people within a given community or workplace; and
- chemical substances or mixtures for which there may be empirical or estimated (i.e., model derived) effects-related data regarding endocrine disrupting potential.

22. The EDSTAC recommends that EPA make use of all available information when evaluating nominations, including anecdotes, and other information gathered as part of the core priority setting process (e.g., information contained within the Endocrine Disruptor Priority Setting Database).

23. To assist EPA in evaluating nominated chemicals, the EDSTAC recommends that EPA request the following types of information from the public regarding nominations:

- how exposure to the nominated chemical substances or mixtures may be disproportionately experienced by identifiable groups, communities, or ecosystems;
- 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
- the degree of support for the nomination from the potentially affected communities and/or workplaces.

I. Endocrine Disruptor Priority Setting Database (EDPSD)

24. The EDSTAC identified and evaluated numerous data sources associated with the exposure and effects information categories and criteria (Appendix G). The Committee endorsed the integration of relevant and useful data sources into a prototype relational database, referred to as the Endocrine Disruptor Priority Setting Database. Although promising, the EDPSD could not be completed within the EDSTAC's time and resource constraints. Consequently, EDSTAC made a number of recommendations regarding continued development and use of the EDPSD.

- EPA should continue to develop and maintain the EDPSD as a tool that can be used to expeditiously sort and prioritize chemicals for endocrine disruption screening and testing.
- The process used by EPA in developing the EDPSD, as well as the process by which it is used, should be open and transparent.
- EPA should convene a multi-stakeholder group prior to the completion of the EDPSD tool to ensure effectiveness, openness, and transparency.
- After completion of the HTPS assays, this group should make use of the tool, along with the "compartment-based" approach to priority setting described below, in assisting EPA as it develops the final priorities for T1S.
- The EDPSD should not be limited to effects data that can be easily placed into a database

format, but should also include data from peer reviewed literature.

- EPA should update the EDPSD at least every six months, and more frequently if time and resources permit.

25. The EDSTAC recommends that EPA provide resources to complete the Quality Assurance/Quality Control 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 data on use 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 FDA Priority Assessment of Food Additives (PAFA) database.

2nd stage: Data on chemical use that were not readily available in databases; chemicals and concentrations of chemicals in National Health and Nutrition Examination Survey (NHANES), Total Exposure Assessment Methodology (TEAM), and Agency for Toxic Substances Disease Registry's (ATSDR) 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.

J. Recommended Approach to Priority Setting

26. The EDSTAC identified a number of obstacles to the development of an "ideal" priority setting system, including the uneven quality and quantity of both exposure- and, even more so, effects-related data sources. Major characteristics of this unevenness include:

- Many more data are available on the effects of the relatively small number of currently registered active ingredients in pesticides (approximately 900) 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 pesticides and frequently rely on engineering estimates rather than actual releases.

27. The EDSTAC recommended several principles to guide the development of a strategy for setting priorities for the large number of chemicals for which there are insufficient data to go to T2T or hazard assessment. The selected system should be transparent, should make use of the guiding principles for exposure- and effects-related data sources, and should be driven by empirical data, but not be held captive by them.

28. The EDSTAC recommends a "compartment-based priority setting strategy" for prioritizing chemicals for T1S.

- The strategy builds upon the identification and evaluation of the different exposure- and effects-related information categories and criteria.
- The term "compartment" refers to the consideration of these information categories either singly or in combination.
- Illustrative examples of the four different categories of compartments include:
  - the integration of exposure and effects information;
  - the consideration of exposure information;
  - the consideration of effects information; and
  - specially targeted priorities (mixtures, nominations, and naturally occurring non-steroidal estrogens).

The specific compartments and the weights and/or order in which they should be utilized have not yet been agreed upon. A target number of chemicals to go through T1S in the first phase of the program or during the life of the program has not been determined. Possible targets and how these targets might be affected by the compartmentalized approach to priority setting have not been agreed upon.

29. The EDSTAC recommends a number of next steps to further develop and refine the compartment-based approach to priority setting, including:

- use of the EDPSD by a multi-stakeholder group to further characterize and define what will be contained in each compartment;
- whether, and if so, how to prioritize the compartments; and
- how to address the possibility of overlaps between compartments.

30. The EDSTAC recommends using the schedule EPA has established for tolerance reassessments and pesticide re-registration under the FQPA for setting priorities for those food-use pesticides that meet the criteria for bypassing T1S and going directly to T2T. When planning for the registration renewal process begins, the FQPA requirement for endocrine disruptor screening and testing should be designated as a criterion for priority setting.

31. The EDSTAC recommends that priorities for T2T for all other chemicals (i.e., non-food-use pesticides and other chemicals where the owner either wishes to voluntarily bypass T1S, or where the owner has met the criteria for completing the alternative, functionally equivalent, T1S assays) should be established on a case-specific basis. However, the EDSTAC recommends that chemicals which receive a high priority ranking for T1S should retain that high priority ranking for T2T, even when the owner wishes to voluntarily bypass T1S.

IV. Recommendations: Chapter Five – Screening and Testing

A. Tier 1 Screening

1. The EDSTAC recommends that any T1S battery designed to detect endocrine disruptors should meet five criteria. The battery should:

- maximize sensitivity to minimize false negatives while permitting an acceptable level of false positives;
- include a range of organisms representing known or anticipated differences in metabolic activity;
- detect all known modes of action for endocrine endpoints of concern;
- include a sufficient range of taxonomic groups among the test organisms; and
- incorporate sufficient diversity and complementarity among the endpoints and assays to reach conclusions based on weight of evidence considerations.

2. The EDSTAC recommends the following assays for inclusion in the T1S battery:

In Vitro

1. Estrogen Receptor (ER)Binding/Transcriptional Activation Assay;
2. Androgen Receptor (AR) Binding/Transcriptional Activation Assay; and
3. Steroidogenesis Assay With Minced Testis.

In Vivo

1. Rodent 3-day Uterotrophic Assay (subcutaneous);
2. Rodent 20-day Pubertal Female Assay With Thyroid;
3. Rodent 5-7 day Hershberger Assay;

4. Frog Metamorphosis Assay; and
5. Fish Gonadal Recrudescence Assay.

3. The EDSTAC identified the following four assays as possible alternatives to some components of the proposed battery and recommends that they also be standardized and validated:

In Vitro

1. Placental Aromatase Assay

In Vivo

1. Modified Rodent 3-day Uterotrophic Assay (intraperitoneal);
2. Rodent 14-day Intact Adult Male Assay With Thyroid; and
3. Rodent 20-day Thyroid/Pubertal Male Assay.

Combinations of the alternative assays, if validated and found to be functionally equivalent, could potentially replace three of the component assays in the proposed T1S battery (*in vitro* steroidogenesis assay with testis, 20-day pubertal female assay, and 5-7 day Hershberger assay) thereby possibly reducing the overall time, cost, and complexity while maintaining equivalent performances of the overall T1S battery. The EDSTAC recognizes that the state-of-the-science in this area is evolving quickly and strongly encourages the use of new or improved assays for screening as they become available.

4. The EDSTAC recommends that validation/standardization studies be conducted on all assays in the proposed battery as well as the alternatives.

5. The EDSTAC agrees that EPA should take affirmative steps, in collaboration with industry and other interested parties, to attempt to develop the protocol for a full life cycle (i.e., with embryonic exposure and evaluation of the adult offspring) developmental exposure screening assay that can be subjected to validation and standardization. The EDSTAC further recommends that, if such an assay were identified, validated, and standardized, the decision on whether it should be included in the T1S battery should include an evaluation of its potential to replace one or more of the recommended T1S assays and its overall impact on the cost effectiveness of the T1S battery.

6. The EDSTAC recommends that all T1S *in vitro* assays involve multiple dose levels, whether performed by HTPS or bench level methods, so a dose-response curve and assessment of relative potencies can be developed. Subject to the results of the validation process, the EDSTAC recommends using one or more dose levels in the performance of the *in vivo* assays.

7. For assessing receptor binding *in vitro*, the EDSTAC is recommending that both the cell-free receptor binding assays and the transcriptional activation assays for ER and AR be incorporated into the T1S battery, and be subjected to validation and standardization.

8. As noted in Chapter Four, the EDSTAC recommends the use of a high throughput pre-screen (HTPS) for toxicants operating though the ER, AR, and TR using stably transfected cell lines with and without metabolic activation, if available. Substances which have not been assessed in the HTPS should be subject to assays for detection of ER and AR activity performed at the bench. Two types of assays are considered acceptable: cell free receptor binding and transcriptional activation in transfected cells. The latter is preferred. Assays must meet the following characteristics:

    - evaluate binding to EAT receptors;
    - evaluate binding with and without metabolic capability;
    - distinguish between agonist and antagonist potential; and
    - yield dose responses to establish relative potency.

9. The EDSTAC is recommending evaluation of antithyroid effects in animals in the longer term rodent screen (either 14-day or 20-day exposure). Although it is not known whether exposure to xenobiotics for greater than 14 days is required to significantly affect circulating levels of T4, TSH, or thyroid histopathology, the EDSTAC believes these longer periods may be required. The effects of duration of chemical substance and mixture exposure must be quickly evaluated in the validation phase.

B. Principles for Evaluating Tier 1 and Tier 2 Results

10. The EDSTAC recommends that a "weight-of-evidence" approach be used in evaluating T1S and T2T results and has developed general criteria for applying "weight-of-evidence" to ensure that decisions are transparent and predictable.

C. Tier 2 Testing

11. The EDSTAC recommends that the following tests be included in the Tier 2 battery:

Mammalian tests

- **Two-generation reproductive toxicity study, or**
- **An alternative less comprehensive test:**
    1. **Alternative mammalian reproductive; and**
    2. **One-generation test.**

Non-mammalian multigeneraton tests

- **Avian reproduction;**
- **Fish life cycle;**
- **Mysid life cycle; and**
- **Amphibian development and reproduction.**

12. The EDSTAC recommends that the "default" action, in absence of any prior information, be to perform all tests in the T2T battery with all endpoints. Further, the EDSTAC recommends that the choice of whether Tier 2 tests will be conducted on all five of the recommend taxa, or a more limited subset of the five taxa, should be based on the physico-chemical characteristics and environmental release and exposure information of the chemical substance or mixture to be tested, together with biological data from T1S. The results of T1S or other information may also allow tailoring of T2T such as the inclusion or deletion of certain endpoints (e.g., thyroid effects) or use of alternative tests.

13. The EDSTAC believes that a project is required to resolve the underlying uncertainties and controversy about issues related to low dose selection and the identification of no-observed-adverse-effect-levels (NOAEL). Further, the EDSTAC recommends that a collaborative group involving government, industry, and appropriate individuals in academia design the study protocols, be kept abreast of the conduct of the studies, evaluate results, and develop overall conclusions and recommendations.

14. The EDSTAC recommends that information used to select doses in the performance of Tier 2 tests include:

- **existing information such as that available during priority setting including the results or the HTPS;**
- **results from T1S;**
- **results from other assays or tests; and**
- **results from range finding studies.**

15. The EDSTAC recommends including thyroid-sensitive endpoints in T2T and that dosing in mammalian tests include fetal and lactational exposure.

D. Validation of the Screening and Testing Batteries

16. The EDSTAC believes the validation and standardization program is of highest priority, and recommends that it proceed on an accelerated schedule. The EDSTAC further recommends that the validation and standardization program be consistent with the principles articulated by the national (ICCVAM, 1996; Zeiger, 1998) and international (OECD, 1996) alternative methods validation groups.

17. The EDSTAC recommends that, as individual screens and tests are validated and standardized, they can be utilized in the EDSTP without waiting for all screens and tests in the batteries to be validated.

18. The EDSTAC recommends that a multi-stakeholder process, involving government, industry, and academics, be utilized in validating and standardizing the T1S and T2T batteries.

19. The EDSTAC identified other screens and tests which, if available, could have an important utility in the screening and testing program, and recommends that research be conducted to determine whether such assays can be developed, and if so, what purpose the assays could fulfill within the endocrine disruptor screening and testing program.

V. Recommendations: Chapter Six – Communications and Outreach

A. Need for Communication

As described in Chapter Two, Section II, the Communications and Outreach Work Group (COWG), and then later the full EDSTAC, recognized the importance of communication about the EDSTP to, among other things, prevent misuse of information. Because the EDSTP applies a tiered approach, results become increasingly definitive as chemicals progress through each step of the screening and testing program. This type of system leaves room for interpretation of results, particularly in the early stages of the EDSTP (i.e., during priority setting or screening), that may or may not be accurate. Therefore, the Committee emphasizes the need for clear and accurate communication to interested stakeholders throughout the development and implementation of the EDSTP. In particular, it is important that EPA clearly communicate about the limitations that must be placed on the interpretation of information and results from the EDSTP, as well as the meaning and implications of its decisions. The recommendations identified in Chapter Six seek to emphasize this point, while providing guidance to EPA as it further develops its communications strategy for the EDSTP.

B. Principles to Guide Implementation of a Communications Strategy

1. The EDSTAC recommends that EPA develop and implement an effective communications and outreach strategy for the EDSTP based on the following set of principles intended to help ensure accurate and open communication to stakeholders:

- **Both the process and results of the EDSTP should be open and transparent.**
- **The results of the EDSTP should be interpreted and communicated within the context set forth in the final EDSTAC Report.**
- **The limitations and uncertainties of the available data and the results of EDSTP should**

be articulated clearly when the screening and testing program is discussed.

- **As new scientific evidence emerges, the uncertainties and limitations of the data may also change. These changes should be communicated clearly.**
- **EPA should develop quality assurance processes to assure that any database maintained for the public relative to the EDSTP is accurate and current.**

C. Basic Features of a Communications and Outreach Strategy

2. The Committee recommends that EPA base their communications and outreach strategy on the following four questions:

- **What should be communicated?**
- **To whom should information be communicated?**
- **How should information be communicated?**
- **When should information be communicated?**

Details of the recommendations for each of the four questions are located in Chapter Six, Section III, B. The basic recommendations, however, follow.

3. Under "What should be communicated?," the Committee recommends that EPA be prepared to provide information to interested stakeholders on the EDSTP itself, on screening and testing results, the nominations process, and background information about the EDSTAC process. Suggested language explaining the various components of the EDSTP in less technical terms than is found throughout the report, is included in the chapter.

4. Under "To whom should information be communicated?," the Committee recommends that EPA actively communicate with members of the public and other stakeholders, such as those who have demonstrated interest in the process through their attendance of the public EDSTAC meetings and public comment periods.

5. The Committee recognizes the need for, and recommends EPA develop, tailored information to be relayed through a variety of mechanisms. This would help to ensure that specific audiences – such as environmental justice organizations, "downstream" industries, farm workers, and patient groups – who may not have the ability to access information via traditional means and who have varying levels of knowledge and interest in endocrine disruptor-related issues, have the opportunity to learn about the EDSTP and its results.

6. The Committee recommends that EPA conduct a follow-up to their September 1997 outreach questionnaire in order to find out more information about how best to

communicate with certain groups, such as those listed above in recommendation number five.

7. Under "How should information be communicated?," the Committee recommends that EPA develop a tracking system as part of the priority setting database described in Chapter Four. They recommend that, if possible, such a database be incorporated into existing EPA systems to promote efficiency and cost-effectiveness. Several characteristics of a desirable database intended to address the needs of a wide range of potential users have been included. The EDSTAC believes it is important for members of the public to have access to information about the screening and testing program as it progresses, including the ability to query and quickly determine the status of a chemical or mixture in the EDSTP, as well as to access and download relevant EDSTP documents.

8. For those without Internet access, information should be available through a variety of sources, including telephone, fax, mail, Federal Register notices, and other forms of communication, as necessary.

9. Under "When should information be communicated?," the Committee recommends that EPA develop a newsletter or bulletin, as has been done in other EPA programs, that would be made available on a regular basis. The report should be of a limited length and should be available for a limited duration.

10. The Committee also recommends that information be communicated when warranted by important EDSTP developments, such as a call for nominations, when lists of chemicals have been prioritized for T1S, identified for T2T, or identified as being subjected to hazard assessment after exhibiting endocrine-mediated adverse effects in T2T, as well as regarding other key decisions relating directly to the program.

11. As described in Chapter Six, Section III, C, the Committee strongly recommends that EPA commit adequate resources to the communication aspects of this program. Several tasks requiring such support are identified in the report, such as the creation and maintenance of a tracking database, maintenance of a Web site with an appropriate graphical user interface, creation and maintenance of a centralized, automated telephone system, and assignment of staff to monitor such items.