Chapter Three

Conceptual Framework and Principles

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I. Introduction

In this chapter the EDSTAC presents the conceptual framework and principles that have served as the foundation upon which all of the other recommendations contained in this report have been built. In addition to this introductory section, the chapter includes sections on: the definition of "endocrine disruptor"; definitions for several other key terms; the purpose and context for endocrine disruptor screening and testing; an overview, scope, and general principles for the framework; the conceptual framework itself; and a discussion of other important conceptual agreements reached after the framework was originally developed.

The initial purpose of the EDSTAC Conceptual Framework was to lay the groundwork for future EDSTAC recommendations and to inform, facilitate, and expedite the work of the EDSTAC work groups. The Principles Work Group developed the original version of the framework in early 1997, and the EDSTAC reached a tentative consensus agreement on the contents of this chapter in May 1997. Subsequently, the document was used by the work groups and the EDSTAC to guide its deliberations. At the time the EDSTAC agreed to the framework's content, members recognized the evolutionary nature of the document and agreed to revisit it, as appropriate, throughout their deliberations.

During the EDSTAC's deliberations, another concept was identified that needs to be considered in the context of the original Conceptual Framework, and other concepts that were already contained within the Framework were clarified. The new concept incorporated into the Framework is the use of "high throughput pre-screening." The concepts further clarified relate to the scenarios under which chemicals would be permitted to bypass Tier 1 Screening (T1S) and the interconnectedness of these bypass scenarios with other elements of the Framework. These concepts are introduced at the end of the chapter and further elaborated upon in subsequent chapters.

In its final version, the EDSTAC Conceptual Framework is intended to provide guidance to EPA regarding development and implementation of its endocrine disruptor screening and testing program, as well as future expansion, if necessary, of the program. All of the draft recommendations contained herein are premised on the principle of scientific validity.

The Conceptual Framework is summarized in the decision flowchart contained in Figure 3.1 which shows how screens and tests are used to evaluate potential endocrine disruptors. The structure of this Framework was placed into tiers to illustrate how chemical substances and mixtures can be sequentially sorted into groups that are increasingly likely to be classified as endocrine disruptors, thereby warranting additional attention.

[NOTE TO THE READER: The text for this section was agreed to at the end of the March EDSTAC plenary meeting. Because of the number of revisions made to prior versions, we

have not included an underline/strikeout of these prior versions in this draft.]

II. Description of Endocrine Disruptor

In any emerging scientific specialty area, numerous terms and definitions are used. As examples, *environmental estrogens, environmental hormones, endocrine disrupting chemicals, endocrine modulators, endocrine disrupters,* and *endocrine disruptors* may all be found in recent scientific publications. Several definitions of *endocrine disruptor* have also been published (Kavlock et al 1996, European Commission 1996, US EPA 1997). Tattersfield et al (1997) distinguished between *endocrine disruption* (reduction or enhancement of hormone levels beyond natural bounds) and *endocrine modulation* (adjustment within natural bounds), but viewed the terms as interchangeable for their purposes. This ambiguity was reflected in EDSTAC deliberations.

In its initial discussions, EDSTAC acknowledged the Kavlock et al (1996) definition as:

> *"An exogenous agent which interferes with the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body which are responsible for the maintenance or homeostasis, reproduction, development or behavior."*

Certain EDSTAC members were concerned that the Kavlock et al definition was formulated for research, and was too open ended for regulatory operations. In May of 1997, EDSTAC developed the following working definition:

"An exogenous substance that changes endocrine function and causes adverse effects at the level of the organism, its progeny, and/or (sub)populations of organisms."

The working definition served a useful purpose in guiding deliberations of the EDSTAC and its work groups. However, over time it became clear that the EDSTAC was divided regarding the acceptability of this working definition.

Two opposing viewpoints emerged. One view held that the definition must include the term *adverse,* whereas the second view held that *adverse* was inappropriate and should be excluded from the definition. Proponents for including *adverse* reasoned that a definition should distinguish disruption from the wide range of hormone fluctuations necessary for normal physiological adaptation. Proponents for excluding *adverse* reasoned that hormone function is so sensitive to xenobiotic challenge, that any biochemical alteration during key developmental stages above background may lead to serious, but subtle pathology later in life or in subsequent generations. In addition, they argued that effects not adverse for an individual may be adverse at the population level. Both sides acknowledged that clear delineation of adverse is at times subjective and may be open to differences in interpretation.

Toxicological effects occur along a continuum from subtle biochemical events to gross pathology. The point at which an observable effect becomes truly adverse is therefore a judgment that may differ among individual scientists.

EDSTAC acknowledges that at this time, knowledge and experience in endocrine disruptor toxicology do not permit the simple categorization of all endocrine effects into *adverse* and *non-adverse*. The capacity to make this distinction will improve as understanding of the assay systems and long term consequences of endocrine effects increases.

In order to achieve consensus, EDSTAC agreed to the following general description to express the range of member's views within the context of the proposed screening and testing program:

> "*The EDSTAC describes an endocrine disruptor as an exogenous chemical substance or mixture that alters the structure or function(s) of the endocrine system and causes adverse effects -- at the level of the organism, its progeny, populations, or subpopulations of organisms -- based on scientific principles, data, weight-of-evidence, and the precautionary principle."*

References

Kavlock, R.J., et al., 1996. Research needs for risk assessment of health and environmental effects of endocrine disruptors: A review of the U.S. EPA-sponsored workshop. Environ. Health Perspect. 104:715-740.

European Commission. 1997. European Workshop on the Impact of Endocrine Disrupters on Human Health and the Environment. Environment and Climate Research Programme, DG XII, European Commission, Report EUR 17549.

Tattersfield, L., et al (Ed.). 1997. SETAC-Europe/OECD/EC Expert Workshop on Endocrine Modulators and Wildlife: Assessment and Testing. SETAC-Europe, Brussels.

U.S. EPA. 1997. Special report on Environmental Endocrine Disruption: An Effects Assessment and Analysis. Office of Research and Development, EPA/630/R-96/012, Washington D.C.

III. Definition of Other Key Terms

The EDSTAC agreed to utilize the following definitions in the Report:

"Priority setting" is defined as the collection, evaluation, and analysis of existing relevant

information to determine whether, and in what relative order of priority, chemical substances or mixtures will be subjected to screening, testing, or hazard assessment.

[NOTE TO THE READER: The following suggested revisions to the definition of screening and testing, along with the corresponding revisions to the statements of purpose for T1S and T2T, grew out of an assignment made at the March EDSTAC plenary. These proposed changes have not yet been reviewed or approved by the full Committee. In addition, these revised definitions and statements of purpose are related to other unresolved issues noted in Chapter Five.]

"Screening" is defined as the application of assays to detect the potential for endocrine disrupting properties of chemical substances and mixtures determine whether a chemical substance or mixture may interact with the endocrine system.

"Testing" is defined as a customized combination of tests andor endpoints designed to determine whether a chemical substance or mixture exhibits endocrine-mediated adverse effects and to identify, characterize, and quantify these effects.confirm, characterize, and quantify the outcome(s) of endocrine disruption.

"Hazard assessment," as used in this document, includes: 1) identification of the chemical substances and mixtures that have endocrine disruption effects, which is often referred to as "hazard identification," and 2) establishment of the relationship between dose and effect, which is often referred to as "dose-response assessment." For an elaboration on how these terms relate to the ecological realm, see Section III below.

"Chemical substances," as used in this document, include naturally occurring and synthetic chemicals and elements. "Mixtures" refers to commonly found combinations of chemical substances, including those found in the environment.

The term "functional equivalency" is used at several critical junctures in the document. The EDSTAC defines an assay, test, or endpoint as being "functionally equivalent" to a T1S or T2T assay, test, or endpoint when it provides equivalent information for each endpoint being studied. For purposes of the ED screening and testing program, EDSTAC-recommended assays, tests, and endpoints must be validated and standardized prior to EPA's use of functionally equivalent information. As discussed elsewhere in this document, EPA should provide clear guidance on the use of functionally equivalent assays, tests, and endpoints prior to the implementation of the screening and testing program.

In general, the term "weight of evidence" is typically used to refer to a process by which trained professionals judge the strengths and weaknesses of a collection of information to

render an overall conclusion that may not be evident from consideration of the individual data. Further clarification of how "weight-of-evidence" principles will be applied to the EDSTP can be found in Chapter Five, Section IV.

IV. Purpose and Context for Endocrine Disruptor Screening and Testing

Language in the Safe Drinking Water Act (SDWA) Amendments of 1996 and the Food Quality Protection Act (FQPA) requires EPA to:

> *"develop a screening program, using appropriate validated testing systems and other scientifically relevant information, to determine whether certain substances may have an effect in humans that is similar to an effect produced by naturally occurring estrogen, or such other hormonal effect as the Administrator may designate."*

The SDWA and FQPA call for EPA to develop a screening and testing program that focuses on chemical substances found in drinking water or food, respectively. Prior to passage of these laws, EPA had already initiated action to create a screening and testing strategy that would address a broad array of human health and environmental protection concerns related to endocrine disruption. These efforts were based on a variety of statutory authorities such as TSCA, FIFRA, and the Clean Water Act. The Committee further recognizes that the endocrine disruptor screening and testing strategy must be designed to be of value to a large number of agencies charged with implementing a broad array of statutes related to the protection of human health and the environment.

Thus, the EDSTAC Conceptual Framework was developed with the recognition that screening and testing data, along with other information, are needed to evaluate both hazards and risks in order to protect human health and the environment. The Committee further recognizes that endocrine disruptor screening and testing data will have relevance to and value for a broad variety of purposes and actions. Given different points of view about competing approaches to decision-making, the Committee has decided to maintain its focus on the development of consensus recommendations on an endocrine disruptor screening and testing strategy that can serve a variety of decision-making needs and purposes.

The Committee, therefore, recommends that the purpose of an endocrine disruptor screening and testing strategy is to identify and characterize the hazards associated with chemical substances and mixtures that disrupt endocrine functions in humans, wildlife, and other biota. In combination with other information, screening and testing data will be used by a broad

array of governmental and non-governmental decision-makers to direct both public and private resources toward those chemical substances and mixtures that pose the highest probable risk to human health and the environment.

The National Academy of Sciences (NAS) risk assessment conceptual framework includes several distinct components. The Committee wishes to make it clear that screening and testing data will be used in the hazard identification and dose-response assessment components of the NAS human health risk assessment framework. While general exposure data will be of value in setting priorities for screening and testing, formal exposure assessment is separate and distinct from hazard assessment. Thus, the screening and testing strategy cannot provide information about the levels of human or environmental exposure.

In the ecological realm, the hazard identification and dose-response assessment steps are conceptually and procedurally similar to how these concepts apply in the human health realm. However, in ecological risk assessment, hazard assessment is termed effects assessment and dose-response assessment is incorporated into effects assessment or, often, into risk characterization. More importantly, the ecological risk assessment framework routinely goes beyond organisms and populations to include effects on communities and ecosystems.

The Committee recognizes there are many different and valid approaches to decision-making. By placing the EDSTAC Conceptual Framework into the larger context described above, the Committee does not wish to endorse any specific approach to decision-making. Nor does the Committee wish to endorse any of the methodologies currently being used to implement one or more of the different components of the NAS risk assessment process.

Finally, the Committee recognizes that voluntary risk reduction and risk management actions may occur independently of the EDSTAC screening and testing strategy. Such voluntary actions might include, but are not limited to, decisions by companies to stop development of a new chemical or pesticide prior to registration or marketing, or the withdrawal of an existing chemical or pesticide from the marketplace. The Committee recognizes the critical importance of both voluntary and statutorily derived efforts to protect human health and the environment. However, the EDSTAC framework does not address the intricacies of either the voluntary or regulatory decision-making processes which will be informed by screening and testing.

V. Overview of the EDSTAC Conceptual Framework

The EDSTAC Conceptual Framework places activities in an ordered sequence. The elements of this sequence include: a) **priority setting**, which includes the sorting and prioritization of chemical substances and mixtures for evaluation in screening and/or testing batteries; b) **screening** to detect chemical substances and mixtures capable of acting on endocrine systems; and c) **testing** to confirm, characterize, and quantify the nature of the endocrine disrupting properties of the chemical substances and mixtures identified by prior information and/or T1S.

The Conceptual Framework contains a series of decision points. At each of these points in the process, all available information is evaluated to determine whether and how to proceed to the next step(s). A "weight-of-evidence" approach is commonly used to make such a determination.

Three guiding principles should be adopted in the use of such a tiered decision-making system:

- This ordered sequence should not exclude the possibility that a chemical substance or mixture could bypass one or more tiers when information warrants such a move (e.g., sufficient prioritization data on endocrine disrupting properties may be available to initiate Tier 2 Testing (T2T) or hazard assessment).

- If information is not adequate to determine whether a chemical substance or mixture should move to the next tier, there should be an active process for generating the information needed to make such a decision.

- The criteria and default assumptions for deciding whether chemical substances or mixtures move from one tier to the next, to the degree possible, should be developed in advance of initiating a screening and testing strategy.

VI. Scope of the EDSTAC Conceptual Framework

The Conceptual Framework is consistent with several central issues defined in the scope of activity for EDSTAC:

- Screening and testing should be relevant to both human health and ecological effects.

- Screening and testing should initially emphasize identifying and characterizing effects that enhance, mimic, or inhibit estrogenic- , androgenic- , and thyroid hormone-related processes. EPA should consider tests that detect multiple hormone interactions, address endpoints in multiple species, and predict long-term or delayed effects. EPA should periodically revisit the scope of this strategy to permit inclusion of additional hormone systems, animals other than vertebrates, other hormone-mediated effects, or new screens and tests as they become available.

- Screening and testing should be capable of evaluating the endocrine disrupting properties of both chemical substances and common mixtures, allowing determination of possible additive, synergistic, or antagonistic effects caused by interactions among the components of the mixture.

VII. Where Endocrine Disruption Fits in the Broader Context

[NOTE TO THE READER: As per the agreement reached at the March plenary, theVenn Diagram figure that had previously been included in this section has been removed. Other changes have been made to be consistent with this change, as well as other assignments made at the meeting. What was the last paragraph in the 3/17 draft has been edited as per an assignment, and moved up to be the second paragraph.]

Many of the effects of endocrine disruption are manifested as disease processes that are previously recognized and addressed, to some degree, in current toxicological assessments. For example, endocrine disruption may result in cancer, neurotoxicity, or reproductive or developmental toxicity (i.e., infertility, birth defects, etc.). It is important to realize that these

issues are interconnected. For example, some cancers have their origin in prenatal life as do some neurological problems. In addition, there may be some endocrine disruptive effects that may not fit clearly into any of the three more well recognized categories.

While considering the potential adverse human health and environmental effects of endocrine disruption, iIt should also be noted that the effects of human exposures to endocrine active chemicals are not necessarily adverse. Knowledge of the functioning of human endocrine systems has led to the development of numerous important medical applications of therapies that operate through chemical modulation of endocrine systems. The applications represent the positive effects of human exposures to endocrine active agents. Examples include: birth control; adjunct therapies for prostate and breast cancer; prevention of postmenopausal osteoporosis and heart disease; treatment of hypothyroidism; induce labor; and prevention or reversale of hair loss. In addition, the consumption of a diet high in soy (and its phytoestrogens) is thought to contribute to low breast cancer rates in some Asian populations. It must be kept in mind that endocrine active chemicals with beneficial effects may still lead to adverse effects under circumstances of unintended, in appropriate, or environmental exposures.

The scope of the program recommended by the EDSTAC addresses a small portion of all possible the hormonal effects depicted in Figure 3.1. Our scope includes disruption of estrogenic, androgenic, and thyroid hormonal activities. This group of hormones includes those for which there exists the most data, and for which standardized assays have been developed. These hormonal systems are a very limited part of the potential universe of endocrine systems in all animals that may be affected by chemical exposures. It is important, as the science evolves, for EPA to be creative in developing and including new screens for additional modes of action or to use different modeling systems that will improve our ability

to detect endocrine-mediated environmental hazards, especially for non-mammalian species. that new screens and tests about other endocrine endpoints, which may be affected invertebrates (e.g., parathyroids, adrenal, pancreas, pituitary hormones, growth factors, retinoids, etc.) as well as invertebrates, be developed in the future.

While estrogen, androgens, and thyroid hormones are extremely important, and it is critical to focus initial development of screens and tests to look for effects on them, the Committee wants it to be clear that the scope of the EDSTP is quite limited. We have not devised a way to test for all possible endocrine disruptive effects, nor are we addressing the many non-hormone-mediated causes of cancer, neurological toxicity, and toxicity to reproduction or to early life stage developmental processes. When a chemical proceeds to the "hold" box of the Conceptual Framework, it is because the chemical tested negative for the hormone systems assessed and not for all hormonal effects or for other mechanisms that may cause these effects.

EPA has already developed toxicological screening and testing protocols to evaluate carcinogenicity, developmental and reproductive toxicity, and nuerotoxicity. Some of the information developed from these screening and testing activities will be useful in evaluating the endocrine disruption potential of chemicals substances and mixtures. For example, results from developmental toxicity testing could suggest the need to undertake T1S or T2T. Similarly, results from screening and testing related to endocrine disruption could suggest the need for neurotoxicity, development, or other toxicity screening or testing. The EDSTAC recommends that EPA examine the interrelationships between these screening and testing protocols and take advantage of potential opportunities to streamline protocols and ensure that the results of the related screens and tests are taken advantage of in assessing the risk of endocrine disruption.

VIII. General Principles to Guide the Development of the Endocrine Disruptor Screening and Testing Program Strategy

Several principles have guided the development of the EDSTAC Conceptual Framework, and should guide further development of specific processes to sort and prioritize, screen, and test chemical substances and mixtures for endocrine disruption. These principles help ensure that the strategy of screening and testing will serve the general purpose stated above, while recognizing that societal resources must also be allocated to sources of environmental risk other than endocrine disruption. Thus, the screening and testing strategy 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;

- be dynamic in order to stay current with the rapidly evolving science related to the endocrine system; and

- be conducted at a minimal cost necessary to make the decisions within the EDSTAC Conceptual Framework.

In addition to these eight broad principles, which place screening and testing for endocrine disruption into a larger framework of environmental risk, there are several principles specific to the screens and tests themselves:

- To make decisions within the EDSTAC Conceptual Framework, all screens and tests should have well-defined endpoints.

- The use of animals should be reduced to the minimal 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 a relatively higher value is placed on sensitivity as opposed to specificity. The goal is to minimize false negative results while also ensuring that false positive results do not become so frequent that chemical substances cannot be sorted meaningfully with respect to with tier 2 testing is needed.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 statistical significance (e.g., necessary confidence intervals) and biological plausibility, should be clearly defined.

IX. The EDSTAC Conceptual Framework

A. Obtain and Analyze Existing Information to SET PRIORITIES

An ordered screening and testing strategy should begin with an effort to obtain and analyze available information on new and existing chemical substances or mixtures. Information on toxic and physiological effects, chemical structure-activity relationships (SARs), use information, product chemistry, exposure information, and legal mandates will be examined. Given limited resources and capacity, as well as the potential magnitude of the task, it will be necessary to develop a priority setting system to determine the relative order in which chemical substances and mixtures will be subjected to T1S. An evaluation and analysis of this information will lead to one of four possible determinations:

polymers which will be placed into a "hold" status (with some exceptions) pending a review of their monomers and oligomers;

chemicals for which there is not sufficient 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.

B. Tier 1 Screening to Detect Interactions with the Endocrine Systemthe Potential for Endocrine Disruption

The purpose of T1S is to obtain a minimum, yet sufficient, set of valid and reliable data to detect whether a chemical substance or mixture may interact with the endocrine systemthat enables classification of chemical substances and mixtures as likely or unlikely to possess endocrine disrupting properties. Included in T1S is a battery of assays designed to detect effects that enhance/mimic or inhibit estrogenic- , androgenic- , and thyroid hormone-related processes. In contrast to the more refined and detailed tests of Tier 2 , the 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 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.

Information gathered during T1S should be used to make initial judgments about areas of concern and should direct and focus 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. Based on the evaluation made during this phase, one of two decisions is possible.

1. Proceed to T2T -- If the interpretation of results from the full battery of T1S assays is determined to be "positive" (i.e., the screens produced evidence of interaction with the endocrine system, endocrine disrupting potential within the scope of endocrine functions addressed by the program), the chemical substance or mixture will enter T2T to characterize the nature of anythe endocrine disrupting effects.

2. Hold Screening and Testing -- If the interpretation of results from the full battery of T1S assays is determined to be "negative" (i.e., the screens have not produced evidence of interactions with the endocrine system, endocrine disrupting potential within the scope of endocrine functions addressed by the program), and these results are not contravened by the "weight of evidence" developed during the prioritization phase, no additional screening or testing is necessary unless:

existing statutes require periodic review (e.g., FIFRA re-registration);

new statutory requirements mandate review;

new screens for endocrine disruption are incorporated into the strategy and it is determined that these new screens may either generate significant new information or they invalidate prior screens and therefore warrant the re-screening of chemical substances and mixtures that have already been subjected to T1S; and/or

new information on the endocrine disrupting potential of the chemical substance or mixture becomes available which warrants re-screening.

C. Tier 2 Testing to Confirm and Characterize Endocrine Disruption

The purpose of T2T is to characterize the nature, likelihood, and dose-response relationship of endocrine disruption in humans and wildlife. Selection of Tier 2 Tests should be based upon T1S results and other relevant information. An underlying principle of T2T is that it should provide information useful for human/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 practical. 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.

- In comparison to the components of the T1S phase, T2T should ideally be both sensitive and specific. In other words, they should be designed to minimize both false positive ("Type I") and false negative ("Type II") errors. Additionally, this battery of tests should:

- include assessment of endpoints identified as relevant from T1S;

- 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 "gold standard" once it is identified.

Interpretation of results from T2T should reflect current scientific judgment, including considerations such as "weight of evidence" and consistency of the data set.

A "negative" result in T2T should abrogate any additional endocrine screening and testing for that particular chemical substance or mixture unless:

a) existing statutes require periodic review (e.g., FIFRA re-registration);

b) new statutory requirements mandate review;

c) new screens or tests for endocrine disruption are incorporated into the EDSTAC strategy which will generate significant new information, or

invalidate prior screens or tests upon which decisions have been made to stop screening and testing ; and/or

d) new information on the endocrine disrupting potential of the chemical substance or mixture becomes available and it is determined that this new information warrants additional testing.

In the event of a "positive" outcome, the chemical substance or mixture will proceed to the hazard assessment phase of decision-making, whereupon it may be decided that additional T2T are required before a final determination of hazard can be made.

X. Additional Components and Clarifications to the EDSTAC Conceptual Framework

During the course of its deliberations, the EDSTAC identified an additional concept, the incorporation of "high throughput pre-screening, which needs to be considered in the context of the original Conceptual Framework. In addition, the EDSTAC clarified conditions under which a chemical substance might be permitted to bypass T1S assays and, instead, go directly to T2T. These two issues are closely connected to other issues discussed later in the report, including testing at low doses and the definitiveness of T2T.

A. High Throughput Pre-Screening

During its deliberations the EDSTAC concluded that biological effects data were incomplete or lacking for most chemical substances. Exceptions to this conclusion are food-use and consumer pesticides and many high production volume chemicals or chemicals for which exposure is widespread (with the exception of fooduse and consumer pesticides). In the absence of biological effects data, EPA would be left with the choice of either raising or lowering the priority of a chemical based on the lack of information.

To address this problem, the EDSTAC recommends that a subset of the *in vitro* assays that are recommended for inclusion in the Tier 1 Screening battery should be conducted with the assistance of automated technology, in advance of the priority setting step of the overall sorting and priority setting process. The EDSTAC came to refer to this technology, which uses robotics and other automated processes, and the role that it will play in the overall endocrine disruptor screening and testing program, as "high throughput pre-screening."

It is important to note that HTPS results will not be sufficient to make a definitive determination about whether a chemical does or does not have endocrine disrupting properties or is not an endocrine disruptor. This is the function of Tier 2 Testing.

The primary purpose of the HTPS is to provide preliminary biological activity information for a large number of chemicals in a relatively short period of time. This information will simultaneously be of value for: a) detecting hormonal activitypotential endocrine disruptors (as a component of T1S); and b) providing at least some biological effects-related information for the estrogen, androgen, and thyroid hormonal systems to assist in the effort to set priorities for T1S. The *in vitro* assays that would be performed as part of the HTPS include transcriptional activation and/or receptor binding assays. Performance of these assays would still be required as part of T1S for all chemicals that do not go through HTPS.

The EDSTAC further recommends that HTPS should be conducted on all chemicals currently produced in quantities over 10,000 lbs. per year. EPA estimates that there are approximately 15,000 chemicals that will meet this criterion. The EDSTAC also recommends that all chemicals that are considered for bypassing T1S should be required to complete the assays that will be part of the HTPS. The HTPS concept is explained in more detail in Chapter Four, Section V. and referred to often in Chapter Five.

B. Alternative Means of Meeting Versus Bypassing Tier 1 Screening

The EDSTAC expects the vast majority of chemicals included in the EDSTP will go through the program in the logical, hierarchical manner for which the program was designed. Notwithstanding this expectation, the EDSTAC recognizes there will be circumstances where it may be inefficient to follow all steps of the EDSTP. For example, the EDSTAC Conceptual Framework allows chemicals that have already been subjected to tests that are the "functional equivalent" of the two-generation tests, endocrine disruptor endpoints, taxa, and dosing considerations recommended by the EDSTAC for T2T to bypass both T1S and T2T and go directly to hazard assessment.

The EDSTAC has identified two other circumstances where a chemical substance may not be required to perform the assays included in the recommended T1S battery. Each of these scenarios are discussed below and then in further detail in Chapters Four and Five.

1. Alternative Means to Meet T1S Information Requirements

The EDSTAC recommends that it should be permissible to complete the information requirements of T1S through the submission of data that are "functionally equivalent" to the

data that would be generated from the recommended T1S battery. Further, functionally equivalent information could be submitted for one or more of the recommended T1S assays or for the entire battery. The EDSTAC believes it is helpful to distinguish this scenario, which is in essence an alternative means of meeting the information requirements associated with T1S, from two other scenarios, which are considered bypassing T1S.

2. Bypassing T1S

The May 1997 draft of the EDSTAC Conceptual Framework included the possibility of bypassing T1S and going directly to T2T. It did not, however, provide clarity as to the circumstances under which it would be permissible to do so, and the implications for completing the information requirements for T2T under these different circumstances.

There are two scenarios in which the EDSTAC recommends the owner of a chemical should be permitted to bypass T1S. Each of these scenarios has different implications for the information requirements associated with completing T2T and hazard assessment following T2T.

Chemicals That Have Previously Been Subjected to Two-Generation Toxicology Tests

The first scenario includes those chemicals that have previously been subjected to mammalian and wildlife developmental toxicology and/or reproductive testing, but such testing may not include additional endpoints for T2T, as specified in Chapter 5, Section VI.two-generation toxicology testing but such testing did not include all of the endocrine disruptor endpoints now recommended for T2T. The EDSTAC expects that food-use pesticides will fall under this heading, given the requirements of FIFRA, as well as a small number of other types of pesticides and industrial chemicals. The EDSTAC agrees that chemicals that meet this criterion for bypassing T1S would still be subjected to the assays that will be part of the HTPS, for the reasons discussed below. In addition, chemicals that meet this criterion will also be the most likely candidates for the alternative approaches for completing T2T, as discussed in Section VII. C. of Chapter Five.

b) Chemicals for Which There is No Prior Toxicology Testing

The second scenario includes those chemicals for which where the owner of the chemical has decided to voluntarily go to T2T achieve the definitive results of T2T without having completed the full T1S battery or any prior two-generation reproductive toxicityology testing. These chemicals must be evaluated in the HTPS assays.will also be required to complete the assays that will be part of the HTPS. In addition, chemicals that bypass T1S under this second scenario must be evaluated in would be required to complete all the tests of the in T2T battery (i.e., the mammalian and non-mammalian multi-generation tests with all the recommend endpoints), consistent with the principles governing T2T, which are set forth in Section V. B. of Chapter Five.

C. Relationship Between HTPS, Bypassing T1S, Low Dose Testing, and the Definitive Nature of T2T

In the context of incorporating HTPS into the EDSTAC Conceptual Framework, and achieving a greater degree of clarity regarding the distinction between alternative means of meeting the information requirement of T1S versus bypassing T1S (along with the two different scenarios for bypassing T1S), the EDSTAC addressed two other interrelated issues. These issues are identified here to provide the reader with a preliminary understanding of these interrelationships. These issues are discussed in more detail in subsequent chapters of this report.

The connection between the use of HTPS assays to identify chemicals that may be of concern at low doses, and how these concerns can be addressed as an interim measure during Phase I of the EDSTP, while a concerted research effort on low dose concerns is being completed (see Section V. of Chapter Four and Section V. D. of Chapter Five); and

The connection between the scenarios for bypassing T1S and the definitive nature of T2T (see Section E. of Chapter Five).