December 23, 1996

EPA-SAB-EHC-LTR-97-002

Honorable Carol M. Browner
Administrator
U.S. Environmental Protection Agency
401 M Street, S.W
Washington, DC 20460

Subject: Science Advisory Board Review of the Risk Assessment Forum's draft document *Assessment of Thyroid Follicular Cell Tumors*

Dear Ms. Browner:

In 1988 the Science Advisory Board (SAB), in conjunction with the FIFRA Scientific Advisory Panel, reviewed a position document covering the risk assessment of agents that produce thyroid tumors in laboratory rodents. This document departed from precedent in that it proposed that some thyroid carcinogens were operating through perturbation in thyroid-pituitary function that would show dose thresholds instead of possible low-dose linearity. The Board embraced the Agency's science review of thyroid carcinogenesis and supported the science policy guidance on the risk assessment process, but requested that the Agency provide more details as to the progression in the development of cancer that may underlie a dose threshold. The Board also requested that EPA develop some case studies that demonstrate how the Agency will use information in the risk assessment process for thyroid cancer. In April, 1996, EPA's Risk Assessment Forum completed a draft document updating the thyroid cancer policy and responding to the SAB's earlier request for additional information. The Forum then requested that the SAB review the updated document.

On July 19, 1996 the SAB's Environmental Health Committee (EHC) met in Washington, DC to review the subject draft document. The Committee membership for this review was augmented to include the Chair and one Member of the Scientific Advisory Panel. The meeting was structured around a detailed Charge (Enclosure A) addressing seven major issues. One of these issues (the first) addressed the overarch-

ing consideration of the overall scientific adequacy of the document; the other six dealt with specific technical questions. The following discussion addresses each of these issues in turn.

a) Overall Scientific Adequacy

The Committee was positive regarding the overall scientific adequacy of the policy document. Each of the criteria iterated in the document is supported by a robust science base and supports the basic policy position that a disruption in thyroid pituitary status in the rodent is associated with increases in thyroid cancer risk in a non-linear dose related fashion. There are adequate scientific data in the case studies and in the incorporated science reviews to guide a risk assessor to appropriate conclusions within the context of the proposed policy, but the Committee believes that addressing some of the technical issues raised in the following discussion would improve the utility of the document.

b) Specific Technical Issues

1) Adequacy of the rodent model in relation to human hazard potential

The science underpinning the EPA position is robust and voluminous. The review of the science as presented at the SAB meeting was outstanding. The update since 1988 was expansive and complete. There was a good comparison between primate and rodent responses to thyrotoxic agents; an excellent discussion regarding the role of growth factor(s) in thyroid disease; and an outstanding presentation of a mechanistic explanation of thyroid carcinogenesis as a secondary (compensatory) response to insult. The scientific review and the conclusions present a course of action that is clear, concise and realistic. The definition of antithyroid action for the class of compounds in question is very pointed and notes that the required “evidence” must include: thyroid hypertrophy, changes in hormone levels, specific site(s) of action, a dose correlation, a time correlation, a lesion progression pathway, and structure activity relationships.

There are some minor caveats. Section 1.3 of the draft document would be enhanced by the incorporation of explanatory graphics such as were used in the presentation at the public meeting. It would be useful to emphasize the concept of biomarkers by adding a statement such as “Figure 1 illustrates that several hormones critical to thyroid homeostasis are measurable in circulating blood and can be used as biomarkers of disruption to the homeostatic process. Use of the T_3 (triododo thyro-nine),T_4 (thyroxine), and Thyroid Stimulating Hormone (TSH) appears appropriate. These are the clinical markers used in patient diagnoses and management and are

important in experimental animals as markers. When coupled with the "definition of antithyroid action," presented above, the biomarkers serve as markers of both exposure and effect; however, because of feedback and compensation, it may be necessary to make measurements at critical time periods to show either exposure or effect.

2) Relative sensitivities of rodents and humans

The report takes the position that rodents appear to be more sensitive than humans to the carcinogenic influences of thyroid-pituitary disruptions. The corresponding proposed science policy position is that

> "Evaluations of human thyroid cancer hazard and risk potential that produce thyroid (and related pituitary) tumors from long-term perturbations of thyroid- pituitary functioning in rodents should (a) incorporate considerations about potential interspecies differences in sensitivity, and (b) evaluate the applicability of potential human exposure patterns relative to animal cancer findings."

Requiring consideration of interspecies differences in sensitivity and human exposure pattern is reasonable. Given the proposed and well-justified qualitative presumption that rodent thyroid tumorigens may pose carcinogenic hazards and risks to humans, the evaluations of differing species sensitivity and its impact should be quantitative and data driven. It appears that data may be sufficient for assessments in several cases. For cases where data are inadequate for such an assessment, presumptions of equivalent species sensitivity and equivalent response for similar exposure patterns seem reasonable. A suggestion for the science policy guidance provided on page 7 of the SAB Review Draft would be to begin point number 2 at the bottom of the page with the language:

> "Where data are sufficient to quantitatively assess, evaluations of human thyroid cancer risk from chemicals..."

and to end point number 2 with:

> "In the absence of data sufficient to quantitatively assess species differences, equivalent sensitivity will be assumed."

Evidence suggests increased sensitivity in rodents in nearly all cases. The Committee suggests adding a caveat in this regard to the first sentence in the second

paragraph on page 7 (e.g., ".... but definitive human studies have not been performed... ") and to rewrite the second to the last sentence of that paragraph to state clearly the

position that "However, quantitatively, humans appear to be less sensitive to the thyrotoxic effects of some chemicals than rodents."

In this regard, more care should be taken in the discussion in section 1.4 of the report. Comparisons of rodent and human tumors, both in background incidence, as well as in response to identified disturbances in thyroid functioning, have not been made. Comparable levels of tissue sampling and histological examination of individuals are typically not performed in the rodent bioassay and human epidemiological investigations; the descriptive and analytic epidemiologic investigations to date are also limited by many other factors, and are difficult to compare with rodent findings; and an explanation for comparable background levels of thyroid tumors for rodents and humans in light of the case being made is not given. Because of these variables, the Committee recommends that the following sentence be added to the end of the paragraph at the top of page 5 of the draft document: "These differences between studies in animals and studies in humans with regard to histology and function, as well as the limiting factors in descriptive and analytical epidemiological investigations, emphasize the lack of definition provided by human data and the uncertainties for comparison with animal data." Finally, regarding the discussion of species differences due to pharmacokinetics/half-life on page 6, differences in pharmacodynamics, species size, and relative lifespan need to be considered before statements regarding overall species differences in susceptibility can be made. Although there are observed species differences for pharmacokinetics/half-life, additional differences in pharmacodynamics, species size, and relative lifespan should be considered before statements regarding overall species differences in susceptibility can be made.

3) Importance of thyroid-pituitary status

The draft policy document takes the position that disruption in thyroid-pituitary status may be associated with increases in thyroid cancer risk, and that there would not be elevated risks for antithyroid chemicals under conditions of thyroid-pituitary homeostasis. These positions are reasonable and justified, given that nonlinear dose-response considerations will be incorporated into thyroid (and relevant pituitary) tumor assessments for chemicals that disrupt thyroid hormone economy and have no mutagenic activity relevant to the carcinogenicity. Agents regulated in this manner will have a substantial data base to support the position of anti-thyroid activity resulting in imbalances of the pituitary-thyroid axis. This will include evidence for enhanced thyroid growth

(increased thyroid weights, hypertrophy/hyperplasia of follicular cells); changes in serum thyroid (decreased thyroxine and triiodothyronine) and pituitary (increased thyroid-stimulating hormone) hormone levels; data on the site of action of the compound (direct thyroid effect or extrathyroidal effect on the peripheral metabolism of thyroid hormones); and correlative data that documents doses of the compound that perturb thyroid hormone economy result in appropriate morphologic changes in thyroid follicular cells.

Nonlinear (threshold) considerations would not be applied to thyroid neoplasia dose-response assessments for chemicals operating by mechanisms that do not disrupt thyroid-pituitary homeostasis and where there is an absence of (or inadequate) mode of action data. The four case presentations in the draft document demonstrate clearly how the process will be accomplished with chemicals that act by several different mechanisms.

It is important that any short-term mechanistic studies conducted to determine if a compound has anti-thyroid activity leading to hormonal imbalances be carefully designed and include multiple doses above and below the level producing thyroid tumors in chronic studies. If possible, the final thyroid cancer policy document should include selected literature citations and brief methodological considerations that will assist sponsors in the development of a high-quality, data-rich information base for use in making decisions regarding risk assessment of xenobiotic chemicals that produce thyroid tumors in rodents.

4) Factors affecting antithyroid activity

The report provides seven factors for assessing whether or not a chemical has antithyroid activity and sets the minimal criteria for making such a determination. Thyroid growth and hormone changes are considered to be the *sine qua non* for evidence of antithyroid activity. These changes show that the homeostatic mechanism to control the metabolic role of thyroid hormones has been challenged and the physiological controls are operational. The Committee agrees with this position, but recommends that the following sentence be added to the second paragraph of section 2.2 (next to the last sentence) of the draft document: “It is important to provide for careful timing of the measurements for TSH, T_3, and T_4, because of the compensatory action of the homeostatic mechanism and because the measurements of rodent TSH are variable and a true increase over control levels may be difficult to show after compensation occurs.”

The next most important of the seven factors are the dose correlations. Changes in growth may increase slightly as the homeostatic mechanism is challenged, but it is important to show where the growth curve for the thyroid gland deviates from the normal growth pattern. This shows that the anti-thyroid effect has caused an abnormal response, even though the hormone changes may be normal due to compensation. With regard to the dose-response correlations, the Committee suggests the deletion of Figure A-3 for Compound 1 from the case study presentation. This figure appears to display an inappropriate transformation of data and could be omitted since Table A-7 makes the point adequately.

Although the site of action factor may not be absolutely necessary for documenting anti-thyroid effect, it is important to understand the basis for the adverse effect and the Committee agrees that it should be listed as required evidence.

With regard to lesion progression, the document's position that cellular hypertrophy should be noted as a confirmation of thyroid growth is correct. However, hyperplasia and stages of neoplasia may be difficult to note as they may only be seen near the termination of a chronic study and further studies to show progression may not be necessary.

The other studies listed under factor 6 can be useful, but not necessary, except for reversibility. Reversibility during the early changes of thyroid growth and hormone changes is important, and should be required.

Structure-activity analyses can certainly add strong support to the evidence on a specific compound, and should be noted when available.

5) Margin-of-exposure considerations

The report proposes a default assumption that the significance of human exposure to thyroid carcinogens should be evaluated by margin-of-exposure considerations unless biologically based models and data are available (The margin of exposure is the ratio of an estimate of the critical No Observed Adverse Effects Level (NOAEL) and estimated human exposure). According to the proposed EPA cancer risk assessment guidelines, the margin of exposure will be based upon the lower confidence limit of a dose producing an excess tumor incidence of 10% or lower, not from the NOAEL for tumors. To be compatible with those guidelines, the thyroid cancer policy document should rely on the same procedure. Since there are several biological effects or markers that may impact on tumor production (T_3, T_4, TSH, hyperplasia, thyroid weight), all of

these endpoints should be examined, not just a single " critical" effect" on which a NOAEL is typically based. The important issue is the shape of the dose-response curve in the low-dose region. More than just the NOAELs should be identified. It would be informative to risk assessors to calculate benchmark doses for all important biological effects. Furthermore, the difficulty of measuring some of these "critical endpoints" with precision argues against use of the NOAEL.

In addition, the final document should discuss reasons why the additivity to background argument with low-dose linearity does not apply to rodent or human thyroid tumors. Since there apparently is only a single critical mechanism, increased TSH, this is a possibility. To argue for nonlinearity, it must be demonstrated that homeostasis prevents increases in TSH in sensitive animals or sensitive thyroid cells at low doses of an exogenous chemical.

6) Adequacy and utility of case studies

The Thyroid Risk Assessment Policy Document describes four case studies of hypothetical chemicals that may act as thyroid carcinogens within the proposed framework of chemical carcinogenesis for follicular thyroid tumors in rodents, i.e., either through antithyroid activity or mutagenic activity. Each case study indicates the types of data that might be available on a given chemical and the process that might be employed in assessing their significance for thyroid carcinogenesis. The policy document places emphasis on assessing the site and mode of action of a chemical and on assessing which dose-response relationships might be used to carry out low dose extrapolations in animal studies. The four case studies are described in extensive detail and illustrate very well the range of information that may be available (or not) for potential thyroid carcinogens. Although the four case studies may not cover all possibilities that may occur in practice, they are sufficient for purposes of illustrating the process of assessing the significance of the data for carcinogenesis in rodents and for assessing the type of low-dose extrapolation that might be appropriate in a given scenario. One minor caveat is noted: there is a need to clarify the dose-response relationship between the untransformed dose of Compound 1 and TSH levels as given in Figure A-3 of the document.

The document also provides guidance for using the case study information in risk assessment. This guidance suggests that: a risk assessor attempt to classify a chemical as much as possible by its site and mode of action using the available data and provides information on conducting low-dose extrapolations in animal studies. Overall, the guidance provided by the four case studies is more than adequate and sufficient as an

example of the process. Several minor changes would enhance further the value of the document. The Committee suggests that the document include a brief comment on whether animals with chronic thyroid stimulation (e.g., iodide deficiency, inhibition of thyroid peroxidase) are susceptible to the development of thyroid tumors from additional exposure to any one of the four hypothetical compounds described, and whether this might suggest the need to consider the possibility of a category of susceptible subpopulation in humans. In addition, the four detailed case studies, which are a critical component of this policy document, should be designated as an Appendix to which a reader can readily refer as needed.

We appreciate having been given the opportunity to address these issues, and look forward to receiving your response to our comments.

Sincerely,

Genevieve M. Matanoski

Dr. Genevieve Matanowski, Chair
Science Advisory Board

Dr. Ernest McConnell, Acting Chair
Environmental Health Committee, and
Chair, Scientific Advisory Panel

ENCLOSURES

ENCLOSURE A

THYROID CANCER RISK ASSESSMENT POLICY DOCUMENT CHARGE

In 1988 the EPA Science Advisory Board, in conjunction with the FIFRA Scientific Advisory Panel, reviewed a position document covering the risk assessment of agents that produce thyroid tumors in laboratory rodents. This report departed from precedent in that it proposed that some thyroid carcinogens were operating through perturbation in thyroid-pituitary functioning that would show dose thresholds instead of possible low-dose linearity. The Board embraced the Agency's science review of thyroid carcinogenesis and supported the science policy guidance but wanted more details as to the steps in the development of cancer that may underlie a dose threshold and some case studies that show how the Agency will use information in the risk assessment process. After several false starts, EPA has produced an update of the thyroid cancer policy. The report has been reviewed by the Risk Assessment Forum and a number of outside reviewers (attached). The revised document has been transmitted for evaluation and comment by a combined Science Advisory Board/FIFRA Scientific Advisory Panel review group.

The revised document comprises several parts. The body is composed of a free standing summary of the science which sets the stage for the science policy, followed by the highlights of the case studies. Several attachments support the policy including: Appendix 1 is the detailed 1988 Agency science review, and Appendix 2 is an EPA science update through 1992. Note that a preliminary search of the literature into 1996 failed to find papers that would significantly alter the science policy positions developed in the report. Appendix 3 is an exemplary listing of chemical classes and individual compounds that are known to produce effects upon the thyroid and, finally, Appendix 4 presents four case studies that illustrate the types of mode of action data that may be available and how to use them in risk assessments. A copy of the October 15, 1988 SAB letter to the Administrator on their review of the original thyroid document is included as Appendix 5.

The Agency is interested in comments on each of the following aspects of the document, in addition to any other comments the review group may have:

1. Overall Adequacy

   a. *Do the scientific data provide a creditable basis for the science policy positions?*

   b. *Are the case studies appropriate to serve as illustrative guidance for risk assessors?*

c. *Are the science reviews (especially the update) reflective of current information and adequate for their purpose?*

2. Specific Issues for Discussion:

a. There is ample information in rodents to show that disruption in thyroid-pituitary status leads to thyroid cancer. For humans, however, there is conflicting and incomplete information on the role of thyroid-pituitary imbalance in thyroid carcinogenesis. The document takes the position that the rodent model cannot be totally disregarded in regard to human hazard potential. *Comment on the review of the relevant science and its support of the proposed science policy position.*

b. Assuming the relevance of the rodent model to human cancer hazard potential, the report takes the position that rodents appear to be more sensitive than humans to the carcinogenic influences of thyroid-pituitary disruption. Risk assessors could provide guidance to risk managers as to the interpretation of this information. *Comment on the summary of the state of knowledge regarding potential susceptibility for thyroid cancer development and the proposed science policy position.*

c. The Agency position is that disruption in thyroid-pituitary status may be associated with increases in thyroid cancer risk. Likewise, there would not be elevated risks for antithyroid chemicals under conditions of thyroid-pituitary homeostasis. *Comment on the reasonableness of this science policy position.*

d. The report develops guidance for assessing whether or not a chemical has antithyroid activity. *Comment on the seven factors included and the minimal criteria for making such a determination.*

e. The report proposes a default that the significance of human exposure to antithyroid carcinogens should be evaluated by margin-of-exposure considerations unless biologically based models and data are available. The margin of exposure is the ratio of an estimate of the critical NOAEL and estimated human exposure. *Is this a reasonable position given the state of knowledge? Address the proposed use of certain biomarkers (e.g., TSH levels, hyperplasia) to estimate potential NOAELs for antithyroid activity and for estimating estimates of cancer risk.*

f. The case studies illustrate some of the range of information that may be available for thyroid carcinogens and the ways one may use such informa-

tion in risk assessments. *Comment on the nature, adequacy and completeness of the case studies and of the guidance for using the information.*

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U.S. ENVIRONMENTAL PROTECTION AGENCY
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ENVIRONMENTAL HEALTH COMMITTEE MEETING
July 19, 1996 -- **Thyroid Cancer Policy Document Review**

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