UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

EPA-SAB-EHC-89-004

October 15, 1988

OFFICE OF
THE ADMINISTRATOR

Honorable Lee M. Thomas
Administrator
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460

Subject: Science Advisory Board's review of issues relating to the Office of Research and Development's document "Thyroid Follicular Cell Carcinogenesis" dated May 1988

Dear Mr. Thomas:

The Science Advisory Board's Environmental Health Committee has completed its review of the issues pertaining to the Office of Research and Developments document "Thyroid Follicular Cell Carcinogenesis" dated May 1988 at its meeting July 14-15 in Washington, D.C..

The general overall conclusion of the Committee was that the document was well thought out and articulated clearly. The major recommendations of the Committee include: the addition of illustrative case studies, the provision of a more detailed discussion of the mechanisms involved in each of the stages from hormone imbalance through hyperplasia, and elucidation of the methods and approaches to be used to define thresholds. The discussion could well include more emphasis on concentration estimates as they relate to the classical LOEL/NOEL transitions.

We appreciate the opportunity to conduct this particular scientific review. We request that the Agency formally respond to the scientific advice provided herein.

Sincerely,

Norton Nelson
Chairman, Executive Committee

Richard Griesemer
Richard A. Griesemer
Chairman
Environmental Health Committee

SUBJECT: SCIENCE ADVISORY BOARD'S REVIEW OF ISSUES RELATING TO THE REVIEW OF THE DOCUMENT "THYROID FOLLICULAR CELL CARCINOGENESIS: MECHANISTIC AND SCIENCE POLICY CONSIDERATIONS"

SCIENCE ADVISORY BOARD COMMITTEE: THE ENVIRONMENTAL HEALTH COMMITTEE

DATE OF REVIEW: JULY 14-15, 1988

PLACE OF REVIEW: HOLIDAY INN GOVENOR'S HOUSE, WASHINGTON, D.C.

The Thyroid Panel commends the EPA staff on producing an excellent document. In preparation, a large body of literature was surveyed, interpreted, and summarized. The result is a work of high quality science. The document provides the entire scientific community with a basic reference on issues relating to thyroid follicular cell carcinogenesis. The staff and EPA should be congratulated, and we encourage EPA to continue to support such efforts in the future.

The Thyroid Panel recommends that the report avoid the appearance of selecting the so-called systemic toxicology model (NOAEL, LOAEL, safety factor) in place of the linear multistage model for agents which meet all the criteria described. The Agency is encouraged to consider a range of mechanistic models, and to develop testable hypotheses based on these models. The recent models proposed for receptor-mediated hormone action may be useful.

The Thyroid Panel recommends that the report emphasize the difficulties inherent in defining thresholds for these effects. Measuring circulating hormones is difficult, and there may be substantial individual variations. Organ weight change is unlikely to be a sensitive indicator. Other molecular approaches to markers of early response include measurement of nuclear receptors, receptor synthesis, gene products or protein synthesis. However, these are not well developed for this system, and thus the detection of a true LOAEL/NOAEL may be difficult.

The Thyroid Panel recommends that the report identify and include information on how the specific biological events leading to transformation can be described as threshold phenomena. The threshold for a nongenotoxic, nontraditional carcinogenic event using animal populations of finite size requires knowledge of the underlying mechanisms in the development of models and tools consistent with this knowledge. Statistical design usually considers multiple dose groups and adequate numbers of animals per group. The

mechanistic judgments, in the case of thyroid effects, can usually be made from data on circulating thyroid-stimulating hormone (TSH), triiodothyronine (T3) and thyroxine (T4) levels, thyroid weight, thyroid histopathology, dose and time relations and potential reversibility. The usual carcinogenesis bioassay design does not permit all these observations. Consequently, supplemental studies on pre-chronic mechanistic studies may be required. Adoption of this policy by EPA would be welcomed by the Committee if there were an associated reduction in bioassays and replacement by focused mechanism-oriented work.

The Thyroid Panel recommends that the Report on Thyroid Follicular Cell Carcinogenesis be revised to incorporate two detailed case studies to determine for known environmental contaminants how the threshold occurs. One case study should illustrate hormonally mediated thyroid carcinogenesis and contain dose-response data on the critical disturbances of the thyroid/pituitary feedback loop. This might include TSH, T3 and T4 serum levels, thyroid weight, thyroid pathology and organ function measurements. Using these quantitative measures, estimates of NOAELs and LOAELs for each response can be made. A final risk estimate would be made using an appropriate model. This would illustrate the concepts and approaches outlined in the policy, provide a guide for others to follow, identify data gaps and provide a testable hypothesis.

The Thyroid Panel recommends that the conditions under which the "threshold model" can be applied should be emphasized and expanded in the executive summary of the report. The six points from page 112 of the report should be included in the Executive Summary because they are extremely important considerations and should be highlighted.

The Thyroid Panel recommends that the discussion of mechanisms which may be involved in each of the stages from hormone imbalance through hyperplasia to cancer be clarified. Substantial evidence exists that elevations in TSH can support the stages leading to thyroid hyperplasia. Elevations in TSH can result from decreased thyroid hormone levels in the blood (TH), disinhibition of hypothalmic control of TSH synthesis, and increased catabolism of TH in the liver, or increased biliary excretion of TH. The uncertainty in our knowledge about the actual mechanisms of carcinogenesis needs to be clearly stated, particularly for the steps from hyperplasia through formation of adenomatous nodules and eventual malignant neoplasia of the thyroid. Some or all of these steps may be hormone-sensitive or hormone- dependent. In humans, hormone therapy can reverse the process at the stages prior to formation of nodules.

The Thyroid Panel concludes that although quantitative differences in pituitary/thyroid function (e.g., plasma half-life, protein binding, etc.) exist between animals and

human beings, the two species are qualitatively similar, with the result that rodents can be an appropriate predictive model for man. In response to long-term TSH stimulation, the rodent (especially the rat) thyroid is more likely to undergo hyperplasia that proceeds to the development of adenomas (and less frequently to carcinoma) than is the human thyroid. Follicular cell hyperplasia in humans associated with iodine deficiency, inherited dyshormonogenesis, immune-mediated (Hashimoto's) thyroiditis, and immunoglobulin-mediated stimulation (Grave's disease) are infrequently associated with an increased incidence of thyroid neoplasia. The infrequency of the association is not inconsistent with the hypothesis that pituitary/thyroid hormonal imbalance is important in the pathogenesis of thyroid tumor development, as presented in the report. Thyroid tumors cells in man have TSH receptors (similar affinity and numbers as normal thyroid cells). Exogenous thyroid hormone therapy is a useful adjunct to surgery in the medical management of thyroid cancer in human patients.

The Science Advisory Board appreciates the opportunity to comment on this important document. Again, we congratulate you on the scientific quality and we hope that our comments have helped you address difficult risk management issues.

U.S Environmental Protection Agency
Science Advisory Board
Environmental Health Committee
Thyroid Panel
July 1, 1988

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