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

January 16, 1987

SAB-EHC-87-021

Honorable Lee M. Thomas
Administrator
U. S. Environmental Protection Agency
401 M Street, SW
Washington, DC 20460

OFFICE OF
THE ADMINISTRATOR

Dear Mr. Thomas:

The Environmental Health Committee (EHC) of the Science Advisory Board has completed its review of a draft Health Assessment Document for Polychlorinated Dibenzofurans. The review was conducted through the EHC's Halogenated Organics Subcommittee, whose letter report is attached.

To summarize the Subcommittee's conclusions, the document will require extensive revision before it becomes scientifically adequate for regulatory decision making. The available information on polychlorinated dibenzofurans is scant. For this reason, staff have utilized information about polychlorinated dibenzo-p-dioxins in the assessment. The scientific theory that supports the use of this analogy is sound. Both groups of substances are thought to cause biological effects by binding with different affinities to the same intracellular receptor molecule. However, the draft document assumes this theory for one plausible effect of receptor binding, namely developmental abnormalities, and not for other effects which have been attributed to polychlorinated dibenzo-p-dioxins in previous Agency assessments, such as carcinogenicity. The Subcommittee requests that EPA either assume the same theory for all effects or provide an explanation of why carcinogenic effects do not follow from binding to the receptor.

EPA may lose a current opportunity gain much useful information from studies of certain accidents involving polychlorinated dibenzofuran exposures of persons in other countries. We will appreciate your personal involvement in stimulating further research on this subject by the Federal agencies. We request a written response to our comments.

Sincerely,

Richard Griesemer

Richard A. Griesemer
Chair, Environmental Health Committee

Norton Nelson

Norton Nelson
Chair, Executive Committee

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

December 17, 1986

OFFICE OF THE ADMINISTRATOR

Dr. Richard A. Griesemer
Chair, Environmental Health Commitee
Science Advisory Board
U.S. Environmental Protection Agency
Washington, DC 20460

Dear Dr. Griesemer:

On September 2, 1986, the Halogenated Organics Subcommittee of the Environmental Health Committee of the Science Advisory Board met in Kansas City, KS to review a draft Health Assessment Document for Polychlorinated Dibenzofurans (EPA/600/8-86/018A; June 1986; Review Draft) prepared by the Office of Research and Development (ORD). Because the public comment period had not closed at the time of the meeting, the Subcommittee agreed not to prepare final comments until ORD sent the public comments to the members. These comments have now been received. After the September meeting, the Subcommittee provided twenty-seven pages of detailed technical comments, five reprints and one preprint to aid ORD in completing the document. This letter summarizes the Subcommittee's general conclusions.

Few data are available to EPA to assess the health effects of dibenzofurans, although these substances are important environmental pollutants. Many scientists believe that polychlorinated dibenzofurans are responsible for most of the toxic effects of polychlorinated biphenyls. The challenge to EPA is to prepare a scientifically defensible summary and interpretation of the health risks from this class of pollutants, based on a choice between all reasonable interpretation methods. For the Subcommittee to provide its scientific advice, it is necessary for the members to be able to react to the options and to the Agency's position. Unfortunately, the draft document was in a preliminary state and needs major revision. This situation increased the Subcommittee's difficulty in developing a consensus regarding the calculation of effect levels and/or action levels.

The Subcommittee concludes that animals poisoned by high levels of polychlorinated dibenzofurans exhibit a pathology that is indistinguishable from that of polychlorinated dibenzo-p-dioxins. The mechanism of lethality is not known. However, the mechanism of induction of certain metabolic enzyme activities in the liver by polychlorinated dibenzo-p-dioxins is known to involve binding to a receptor molecule in the cytosolic fraction of cells. Polychlorinated dibenzofurans also induce these enzyme activities. Induction of metabolizing enzymes in the livers of intact animals correlates with lethality for different purified polychorinated dibenzo-p-dioxin-like substances.

These discoveries lead to a hypothesis that many scientists find compelling in the absence of other information, namely that binding to the cytosolic receptor molecule explains all biological effects of these substances. If this is true, then it is reasonable to apply the available information about polychlorinated dibenzo-p-dioxins to an understanding and evaluation of polychlorinated dibenzofurans. All substances in this category would be considered analogues that act by binding to the same receptor with different affinities, subject to modifications for pharmacokinetic properties and interactions with similar substances.

Using the above hypothesis, it is reasonable to attribute all qualitative properties of the most studied analogue, 2,3,7,8-tetrachloro-dibenzo-p-dioxin to different polychlorinated dibenzofurans and to estimate the potency of each polychlorinated dibenzofuran relative to the activity of 2,3,7,8-tetrachloro-dibenzo-p-dioxin. The draft document does not adequately discuss the carcinogenic potency expected of specific polychlorinated dibenzofurans (or mixtures of polychlorinated dibenzofurans), although the Agency's position is that 2,3,7,8-tetrachloro-dibenzo-p-dioxin is a probable human carcinogen, based on the induction of tumors in both sexes of rats and mice. In addition, the final document should provide in-depth discussions of the techniques to derive such dioxin equivalent relative potencies as well as approaches such as the Ahh method of Safe or the flat cell assay of Gierthy, which can provide suitable data.

Effect levels can be calculated either directly, both from animal and human data for polychlorinated dibenzofuran exposures, or indirectly by extrapolating between structurally similar compounds. The draft Health Assessment Document provides estimates of the lowest doses at which toxicity is seen, based on (1) hydronephrosis of the fetal mouse after short-term exposures, and (2) effects in humans after ingestion of polychlorinated dibenzofuran contaminated rice oil. These estimates turn out to be dissimilar (about 0.007 ug/kg·day for humans and 3 ug/kg·day for mice). However, the lowest dose at which toxicity occurred after chronic exposure of rodents to 2,3,7,8-tetrachloro-dibenzo-p-dioxin can be extrapolated to a polychlorinated dibenzofuran equivalent dose of about 0.003 ug/kg·day. The draft document then applies a series of uncertainty factors to the latter estimate to calculate a "risk reference dose" (RfD).

The Subcommittee disagrees with the use of a standard uncertainty factor of ten-fold to extrapolate from animals to humans for the RfD. The known variation in the sensitivities across species is greater than 5,000-fold in the toxic effects of substances in this category. EPA should attempt to identify the actual interspecies equivalency of polychlorinated tricyclic substances from an analysis of the available data before substituting an ad-hoc, default assumption. The quality of both animal and human data that relate directly to polychlorinated dibenzofurans obviously present problems of interpretation in estimating human health risk. The Subcommittee is of a divided opinion regarding the reliability of human versus animal data. Some members prefer the greater control possible with animal experiments; others prefer not to extrapolate from animals to human, whenever any human data are available.

The Subcommittee members all agree that comparison of the animal and human estimates, as the Agency has attempted, is a good approach. However, the consensus opinion is that EPA has not interpreted the available information to the extent desirable. Public commentors have contributed alternative analyses, and one

Subcommittee member has provided an estimate of 0.002 ug/kg•day as the highest (lifetime) daily dose at which no effects were seen in an incident involving humans in Taiwan. Additional estimates can be prepared by taking a creative approach to the available information.

The Agency should be sensitive to the possibility that the scientific assumptions upon which the interpretation in the draft document is based may change. The same receptor molecule may not be responsible for the effects of polychlorinated dibenzofurans in all tissues. The established linkages between the binding and effects (other than arylhydrocarbon hydroxylase induction), which are thought to be the cause of toxicity, need to be discussed more thoroughly and investigated through future research. Further, the possibility of multiple mechanisms of action should be considered.

There is no good reason to expect changes in the available information for polychlorinated dibenzofurans in the near future, particularly in the area of animal bioassays, since scientific research needs will not drive the acquisition of such data. It is possible that regulatory needs might motivate further bioassay work, but the Subcommittee questions whether this drive might not distort priorities elsewhere. However, in the case of the human incidents involving polychlorinated dibenzofuran exposures, a unique current opportunity is being lost through relative inaction. We request that the Chair of the Science Advisory Board and the Administrator personally involve themselves in stimulating further international work by the Federal agencies to investigate these incidents.

We appreciate the opportunity to review this important public health issue and stand ready to review additional information, as requested. Public commentors have made the point that the next version of the document will significantly change from the current draft. The Subcommittee agrees because the Agency clearly will have to make many scientific choices in reaching final conclusions. Nevertheless, the Subcommittee views its objective as one of improving the quality of the draft. It is confident that both its meeting and review have been contructive and that this objective is being accomplished.

Sincerely,

John Doull
Chair, Halogenated Organics Subcommittee

Seymour Abrahamson
Vice-Chair, Halogenated Organics Subcommittee

U.S. Environmental Protection Agency
Science Advisory Board
Environmental Health Committee
Halogenated Organics Subcommittee
Dibenzofurans Panel

September 2, 1986
Kansas City, Kansas

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Executive Secretary

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