MEMORANDUM

SUBJECT: Response to Registrant Comments on the Data Supporting the FQPA 10x Safety Factor Rationale for Endosulfan

FROM: Special Review and Reregistration Division
Office of Pesticide Programs

TO: OPP Public Docket for Endosulfan
Docket #OPP-2002-0262

Introduction:

This document addresses comments submitted by the Endosulfan Task Force (ETF) concerning the reevaluation of the human health risk assessment for the Reregistration Eligibility Decision Document (RED) for Endosulfan, dated May 30, 2002. In particular, concerns regarding the interpretation and presentation of data as it relates to the FQPA 10x Safety Factor Rationale. Please find below a summary of the ETF comments and the Agency's responses.

ETF Comment:

An error was incorporated into the scientific rationale of the human health chapter regarding susceptibility of young animals to endosulfan. This error resulted in excerption of information from the ATSDR *Toxicology Profile for Endosulfan* (Sept. 2000), which reported the data incorrectly.

Agency Response:

The Agency notes that according to the study in question, adult male albino rats were acutely exposed to 1.0 and 3.0 mg/kg/day (p.626 Seth *et al.* 1986). The distinction that the dosing was acute, however, was not made in the human health risk assessment and will be clarified in an addendum to the document.

ETF Comment:

The comparison of effects in three-week-old versus three-month-old rats is made between two separate studies conducted two years apart, not one study. Further, statistical errors were identified in the human health chapter. There was no dose-related difference in effects between three-week-old and three-month-old rats as reported.

Agency Response:

The Agency agrees that two Sinha studies are being referred to in this language and that the use of the wording "In a study' should be changed to read "In two studies." Both studies are referenced in the risk assessment document (Sinha, 1995 & 1997). The Agency has thoroughly reviewed these articles as part of its deliberations regarding the FQPA Safety Factor and has made no statements as to the statistical significance of the observed effects. Nonetheless, the effects are biologically significant and add to the weight-of-evidence. It should also be pointed out that both Sinha studies were conducted in the same laboratory, with the same strain of rat, and under the same laboratory conditions so, it is appropriate to consider the results of the two studies together.

ETF Comment:

Data availability that led to the Agency's FQPA Reevaluation is misleading. In February 2002, when this recommendation was made, all of the data cited by the Agency had been available to the Agency since 1998. The ETF has also noted that the initial toxicology report, submitted to the FQPA Safety Factor Committee in October 1998 by Dr. Liem, stated that there were no additional acceptable studies available in the published literature that would influence a FQPA decision. This information shows that the Agency had performed a literature search in 1998 and was aware of the available data.

Agency Response:

In February 2002, the FQPA Safety Factor Committee (FQPA SFC) convened and reconsidered the data available for endosulfan. At that time, the committee evaluated a review by Dr. David Liem on the potential impact of endosulfan exposure as presented in the published literature. As noted in the document "Supporting Documentation for Findings of the FQPA Safety Factor Committee" dated February 11, 2002, Dr. Liem's evaluation was not available to the FQPA SFC for review during the November 2, 1998 and was not completed until November 24, 1998. The aforementioned review was provided for the first time to the Committee on February 2002 and is therefore an addition to the body of information that was previously reviewed by the Committee.

ETF Comment:

The ETF has never, in any of the four written responses to the Agency, "limited their criteria for endocrine disruption to receptor binding." In all cases, the ETF relied on the current OECD and EDSTAC definitions, which expressly state that the more reliable indicator of endocrine disruption are endpoints derived from *in vivo* test systems. Further, the Agency has indeed hypothesized about the mechanism of action of endosulfan as it relates to hormone levels in rats.

Agency Response:

The Agency will revise the excerpted language in question in order to avoid any confusion as to the ETF position on endosulfan's potential for endocrine disruption. The full text of the comments submitted by ETF will be placed on the internet and in the public docket.

ETF Comment:

It is completely inaccurate that the ETF disagreed with the Agency's use of open literature studies in its evaluation claiming the literature studies have not been thoroughly reviewed. The ETF stated that the Agency should rely on the results of the guideline studies only, which did not detect the effects discussed in the literature studies. The ETF has repeatedly stated that the entire database should be evaluated in order to make a sound scientific weight-of-evidence determination.

Agency Response:

The Agency agrees to modify its language to reflect that ETF is not opposed to the use of published literature as part of a weight-of-the-evidence determination. This position is consistent with the Agency's policy to consider published literature as part of its risk assessment. Further, the Agency has conducted a scientific review of the published literature. When evidence of toxicity is reported in the published literature for parameters not evaluated by the guideline studies, the Agency considers the published data as part of the risk assessment process. In the case of endosulfan, several of the studies in the published literature evaluated parameters not assessed in the submitted guideline studies. The Agency recognizes that there is variability in the results, the experimental conditions (e.g., using different dosing regimens [*in utero exposure versus in utero* and post-natal exposure], the batches of test article, the strains of animal tested [Wistar *vs.* Drukrey], and timing [e.g., 1997 versus 2001] in the published literature studies. These differences, therefore, preclude a meaningful comparison of the findings.

ETF Comment:

The ETF's primary concern, as with most of the human health chapter, is the assessment of the available data. The human health assessment was very selective in its presentation of results. Only positive effects that supported the Agency's position were presented. Other key aspects of the studies were completely disregarded, with absolutely no mention or discussion of endpoints and results that were in opposition to their point of view. Since these are public documents, EPA has an obligation to provide the public with all of the available information, and not just selected parts. This type of biased reporting of data is unprincipled and needs to be corrected.

Agency Response:

The Agency agrees with the ETF's conclusion that the studies in question are important and need to be assessed as part of the weight-of-the- evidence evaluation of endosulfan. The details of the many studies reviewed as part of the Agency's risk assessment are often not included in the risk assessment document itself since all documents and source material related to the risk assessment is either available on the Agency's internet site/public docket or full citations are provided. Rather, the Agency will summarize the key points of the research in its professional judgement and provide the reader with the appropriate citation where additional information can be found. This practice is not contingent on the outcomes of the study in an attempt to be biased but, rather, is a common practice in most Agency risk assessments.

ETF Comment:

The Agency misquoted comments made by the ETF. The following excerption by the Agency

is a direct misquote: “The ETF acknowledged indications of potential disruption of reproductive hormones in males.” “This statement by the ETF reaffirms the Agency’s position of the potential for endocrine disruption by endosulfan.”

Agency Response:

The Agency will modify the excerpted language in question in order to avoid any confusion as to the ETF position on endosulfan’s potential for endocrine disruption. The full text of the comments submitted by ETF will be placed on the internet and in the public docket.

ETF Comment:

The human health assessment contains a biased representation of the available data on endosulfan. This public document consistently includes only data that is supportive of the Agency’s position. For example, there are no full descriptions of published literature studies with all of the data presented. In addition, studies that provided negative findings are not noted or discussed at all. EPA is held to a standard of professionalism that requires unbiased and sound-science based expert judgements of reliable data for every chemical it assesses. Endosulfan has not received this type of assessment, and the public is being presented with a document which is full of biased representation of data that is both inappropriate and misleading.

Agency Response:

The Agency believes that the risk assessment and its conclusions are an unbiased representation of the available data for endosulfan fully incorporating all applicable Agency policies and procedures.

ETF Comment:

The human health assessment has repeatedly cited effects from a 1978 NCI chronic/carcinogenicity study in rats. Details of this study have never been provided in discussions with regard to the FQPA safety factor. The human health chapter does not acknowledge that this study was found to be an unacceptable guideline study. More importantly, the FQPA Safety Factor Committee has never acknowledged that a guideline acceptable chronic/carcinogenicity study in rats exists within the core database for endosulfan, and that this study was negative for the effects of concern.

Agency Response:

The Agency notes that a reference to the acceptable/guideline Combined/Chronic Oncogenicity Study in Rats (MRID 41099502) is in the risk assessment document on pages 33-35 and page 38. The full citation of the NCI study is also provided in the risk assessment.