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

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

7 April 2005

MEMORANDUM

Subject: Transmission of Background Materials for the Session of the May 5-6, 2005 FIFRA Scientific Advisory Panel Entitled "A Comparison of the Results of Studies on Pesticides from 1- or 2-year Dog Studies with Dog Studies of Shorter Duration"

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Attached is the document "A Comparison of the Results on Pesticides from 1- or 2-year Dog Studies with Dog Studies of Shorter Duration" The purpose of this document is to describe a retrospective analysis of the results of dog studies submitted to the Office of Pesticide Programs in support of the registration or reregistration of pesticides. Under the current CFR Part 158 toxicology data requirements, a 90-day and a 1-year non-rodent (dog) study (guidelines 82-1 and 83-1) are required for all food use

pesticides and for pesticides with nonfood uses if use of the pesticide product is likely to result in repeated human exposure to the product over a significant portion of the human life-span. Over the last three decades the Agency has received the results of a large number of dog studies in support of the registration of pesticides. The Agency has conducted a retrospective analysis of dog studies that provided the basis for the selection of reference doses (RfD's) in order to determine whether the requirement for both a subchronic and a chronic dog study continues to be justified. The analysis involved a comparison of the results of 13-week studies and 1- or 2-year studies or a comparison of interim data (90-days or less) from 1-year dog studies with the data from 1-year in the same study. The Office of Pesticide Programs will be soliciting comments from the FIFRA Scientific Advisory Committee on this retrospective analysis of the results of dog studies and, specifically, on the soundness of this retrospective analysis and whether the analysis supports the continuation of the requirement for both subchronic and chronic dog studies or whether consideration should be given to a modification of the current requirements for dog studies (see Charge below).

Attachments:
Document For Review With Respect to Charge–

- ❑ OPPTS March 2005 Draft Document on "Comparison of the Results on Pesticides from 1- or 2-year Dog Studies with Dog Studies of Shorter Duration" (Enclosed)

Background Material–(reprints)

- ❑ EPA is currently obtaining permission from journal publishers to copy articles referenced in EPA's document submitted for review by the SAP. Permission to copy all pertinent articles is expected shortly and copies will the be forwarded under separate cover.

Charge to the Panel:
Please provide comment and advice on the following questions.

Issue 1: Comparison of the results of 13-week and chronic dog studies

OPP has concluded that there is evidence that little qualitative and quantitative value is added by requiring both a 13-week dog study and a 1-year dog study to support the establishment of chronic oral RfDs for pesticide residues.

> **Question 1** - . Please comment on the adequacy of the approach used and the comparisons made regarding the results of dog studies of different durations. OPP would also appreciate recommendations from the panel on improving the analysis (e.g., figures and tables) or, if needed, discussion of additional analyses that would elucidate the validity of the conclusions made.

Issue 2: Examples where NOAELs or LOAELs were found to be lower in chronic dog studies than in 13-week dog studies

Nineteen examples (Table 3, Appendix) were initially identified where NOAELs or LOAELs were found to be lower (≥ 1.5X) in chronic dog studies than in 13-week studies. Further analyses showed that for 11 of these examples, the observed differences seem to be associated with differences in dose selection or inter-experimental variability (interim data from 1-year studies indicated the same NOAELs/LOAELs could be identified at 13-weeks). For the remaining 8 pesticides (Table 1, main text), there are rat studies that would provide comparable NOAELs/LOAELs to the chronic dog study (2 pesticides) and, for 3 pesticides, data were insufficient for an in-depth comparison of the results of 13-week and chronic dog studies or the data were inconsistent with current biological understanding. Finally, three pesticides were identified where results of the chronic dog study seem to be more appropriate for selection of NOAELs/LOAELs that would be used for derivation of a chronic RfD.

Question 2: Please comment on the clarity and soundness of the evaluations presented on the 19 pesticides where NOAELs or LOAELs appeared to differ between the 13-week and chronic studies. Specifically, do theses cases detract from the overall conclusions regarding the value of 1-year dog studies in RfD selection.

Issue 3: Recommended durations for dog studies conducted on pharmaceutical agents versus dog studies conducted on pesticides.

An International Conference on Harmonization (ICH) workgroup recommended that, in the case of pharmaceutical agents, the animal toxicity database should include a dog study of at least 9 months duration (DeGeorge *et al.,* 1999). This recommendation appears to have been based primarily on evidence that additional toxicities were seen from 9-12 months that were not evident at 6-months. EPA understands that such studies are often conducted with dose levels in the range of dosages anticipated for humans. Therefore, such evidence could lead to an adjustment in the pharmacologically active doses that could be used clinically or the additional toxicities could be used in the monitoring of clinical parameters. However, it appears that only in a few cases did the additional toxicities seen in 9-12-month studies led to a revision in the margin of safety (*i.e.,* the ratio of no observed adverse effect level to the anticipated human exposure, in this case exposure to a pharmacologically active dose); it is unclear to what extent margin of safety estimates for pharmaceuticals, in general, would be affected.

EPA's purpose for requiring dog studies conducted with pesticides is to identify a no observed adverse effect level (NOAEL) and the lowest observed effect level (LOAEL, or the lowest dose that produces some biologically significant evidence of toxicity). The effects at the LOAEL are used to characterize the toxicity that may be expected to occur if exposure to a pesticide exceeds an RfD. The NOAEL is used to derive an RfD, which represents a dose that is unlikely to produce adverse health effects in humans exposed to environmental residues of a pesticide at or below the RfD. In contrast, dog studies performed with pharmaceuticals are designed to ascertain

whether adverse effects may occur in humans administered a pharmaceutical chemical at pharmacologic doses and to determine margins of safety.

The analysis of 13-week and 1- or 2-year dog studies conducted on 172 pesticides by Spielmann and Gerbracht (2001) and the results of the analysis of 77 studies on pesticides by the Office of Pesticide Programs has provided evidence that the NOAELs and LOAELs observed in 13-week and 1- or 2-year dog studies generally do not differ. Further, Spielmann and Gerbracht (2001) found that for only 7 of 141 pesticides were significant new effects found in 1- or 2-year dog studies that were not seen in 13-week dog studies or chronic studies with rats. Based on the results of these analyses of dog studies conducted with pesticides, EPA has concluded that a dog study of 13-weeks duration provides sufficient data for an evaluation of potential chronic toxicity in this species along with other routinely required toxicity studies. (Note that a chronic dog study is only one of several studies that may be selected for the derivation of a chronic RfD; other possibilities include a 2-year rat study, a 2-generation rat reproduction study, and an 18-month mouse study)

Question 3A: Given the somewhat different objectives of dog studies conducted on pharmaceutical agents and on pesticides please comment on the extent to which the recommendations of the International Conference on Harmonization workgroup may be relevant to the use of dog studies in risk assessments with pesticides and whether the results of studies performed specifically on pesticides support EPA's conclusion that a dog study of 13 weeks duration along with rodent chronic data is adequate for providing an assessment of chronic toxicity for purposes of deriving chronic RfD's.

Question 3B: EPA's analysis showed that there was no additional qualitative hazard information provided by a 1-year dog study which would raise significant concerns that would lead to the application of uncertainty factors in addition to the standard factors when deriving an RfD. Please comment on the soundness of this conclusion.

Issue 4. Refinement of the 13-week dog study.

The dog, as a second non-rodent species, is well accepted and established as an important regulatory data requirement.

> **Question 4:** If the 13-week dog study is considered adequate for hazard identification, how could the best use be made of this 13-week study to characterize potential human health effects (e..g., increase the number of animals evaluated, measuring additional parameters such as blood pressure and ECG, obtaining toxicokinetic data)?