

Dear Dr. Sustkind

We have reviewed the proposal relating to Toxicology studies with 2,3,7,8-TCDD in monkeys. ~~and we feel that is an important area that should be pursued. Specifically at this time, we would like to emphasize should be placed upon the kinetics of absorption, distribution and excretion of TCDD in rhesus monkeys. This information may help to explain the apparent exquisite sensitivity of this species. Because most previously reported studies with TCDD with primates have used rhesus monkeys, this species should be used throughout these kinetic studies.~~

~~It would appear that the major goals exist to support of the <sup>14</sup>C-TCDD metabolism studies should be:~~ (1) to compare the absorption, excretion, and tissue distribution pattern of acutely toxic and chronically toxic ~~single~~ doses of TCDD and (2) to compare the absorption, excretion and tissue distribution of non-toxic and chronically toxic doses in animals not previously exposed to TCDD and in animals that have reached a steady state relative to a TCDD body burden. CONFIDENTIAL C07462

It may be possible to conduct experiments one and two. Dosages could span an acutely toxic and of 10 ug/kg, a clinically toxic one of 0.1 ug/kg (approximately 5 ppb in monkey diet), and a threshold toxic dose of 0.001 ug/kg (approx. 0.5 ppb in monkey diet) a total of 50 ppb in monkey diet. We feel that a minimum out-pat should be collected for a long enough period to provide data to calculate the body burden and a life. We will try to in rats samples from 8 to 31 days and study also levels we needed in rats.

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After approximately 3 months. It might also be worthwhile to dose groups of rhesus monkeys with 0.001 and 0.1 ug/kg/day ~~at~~ (study dose of the incorporated into a total body burden or apple sauce) for a 3-month period followed by a single 14-1700 dose and continued daily cold doses to determine if retention differed at total body burden increased.

It was suggested that doses are generally lower than those in the original proposal. The lower doses are based upon the in striking data suggesting subacute and chronic toxicity data and doses.

In monkeys Allen has reported severe toxic signs and death after 6 months in monkeys given 0.01 ug/kg/day (500 ppb) in their diet. Later he reported 0.001 ug/kg/day for two years and treatment related effects. In rats reproduction efficiency was decreased in ~~rats~~

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and possibly let end  
live biopsy sample can be obtained  
periodically to develop tissue accumulation  
and disposition. <sup>These</sup> information would  
support the total body function in the  
collected from the nitrogen pattern, and  
might be needed to determine if tissue  
retention patterns should with time.

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determinations  
would be adequate

The number of animals to be used in each  
group will be dependent upon facility available  
and whether or not there are <sup>any</sup> intergroup sacrifices.  
This will also be a major factor in determining  
the cost of conducting these experiments.  
~~It is suggested that a design of the~~  
~~experiment be developed - that the use of~~  
~~prior studies in determining~~  
minimal metabolism of TCDD. Initially  
the would examine and ~~by~~ relatively  
low sample for subjected to ~~any~~  
physiologic changes analysis outlined  
in the ~~first~~ <sup>second</sup> ~~phase~~ <sup>phase</sup> of ~~the~~ <sup>the</sup> ~~study~~ <sup>study</sup>  
→ to eventually ~~the~~ <sup>the</sup> ~~action and~~ <sup>production</sup> ~~recuperation~~  
~~should be~~ <sup>if</sup> ~~coupled with a~~ <sup>coupled with a</sup>  
~~limited~~ <sup>limited</sup> ~~number of~~ <sup>number of</sup> ~~analyses~~ <sup>analyses</sup> to  
confirm the presence of 2,3,7,8-TCDD.

Depending upon the facility availability of facilities, it might also be possible to administer daily doses of  $^{14}\text{C}$ -TCDD to monitor excretion and body burden kinetics. Such an approach would substitute radioactivity analyses for  $^{14}\text{C}$ -TCDD of the urine and feces for  $^{14}\text{C}$ -TCDD for the cold TCDD analysis to establish the time required to reach a steady state. This would also have the advantages of ensuring that all metabolites were accounted for and a reduction in the number of complex chemical analyses which should also reduce the cost of conducting these studies.

Hopefully these suggestions will be useful in establishing a sound experimental program. We would welcome the opportunity to discuss this with you, with others whom you might suggest.

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