

Dear Dr. Sustkind

We have reviewed the proposal relating to Toxicology studies with 2,3,7,8-TCDD in monkeys. ~~We feel that this 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, we believe this species should be used throughout these kinetic studies.~~

~~I would appear that the major goals of the 14 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 607462

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It may be possible to combine experiments one and two. Dosages could span an acutely toxic one of $10 \mu\text{g}/\text{kg}$, a chronically toxic one of $0.1 \mu\text{g}/\text{kg}$ (approximately 5 ppb in monkey diet), and a threshold toxic dose of $0.001 \mu\text{g}/\text{kg}$ (approximately 50 ppt in monkey diet). Total feces and urine output should be collected ^{daily} for a long enough period to provide data to calculate total body burden and half-life. The half-life in rats ranges from 13 to 31 days and steady state levels are reached ~~in rats~~

after approximately 3 months. It might also be worthwhile to dose groups of rhesus monkeys with 0.001 and $0.1 \mu\text{g}/\text{kg}/\text{day}$ ~~these~~ (daily doses ^{could} be incorporated into a treat such as banana or apple sauce) for a 3-month period followed by a single ^{14}C -TCDD dose and continued daily dose to determine if retention differed ~~at~~ so total body burden increased.

~~These suggested~~ ~~low~~ doses are generally lower than those in the original proposal. ^{The basis for recommending} these lower doses are based upon ~~the~~ is existing data suggesting subacute and chronic toxicity data ~~low~~ doses. In monkeys, Allen has reported several toxic signs and deaths after 6 months in monkeys given $0.01 \mu\text{g}/\text{kg}/\text{day}$ (500 ppt) in their diet. Rats fed ~~more~~ than $0.001 \mu\text{g}/\text{kg}/\text{day}$ for two years had treatment related effects. In rats reproduction efficiency was decreased in ~~rats~~

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about ~~samples~~ and possibly but not
less biologically samples can be obtained
periodically to develop trends accumulation
and dispersion. ~~information~~ ^{information} would
assist the ~~total~~ ^{total} by ~~providing~~ ^{providing} it
collected from the collection pattern and
might be needed to determine if trends
attention patterns should with time.

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The number of animals to be used in each
group will be dependent upon facility availability
and major or not where interim experiments.
This will also be a major factor in determining
the cost of conducting these experiments.

~~These experiments should be done in a~~
~~facility which is not a laboratory and where~~
~~possible to obtain results - study the use of animals~~

determinations
would be adequate

Prior to this is demonstrated by
minimal metabolism of TCDD, probably
~~the~~ would require ~~but~~ ^{by} relatively
low samples for ~~subjected~~ ^{subjected} to ~~the~~
optimum chemical analysis outlined
in the report. ~~The~~ ^{the} ~~process of~~ ^{Radioactivity}
to quantify ~~the~~ ^{of} ~~action and~~ ^{excretion} ~~excretion~~.
~~as well as~~ ^{as well as} ~~if~~ ^{if} ~~coupled with a~~ ^{coupled with a}
~~limited~~ ^{limited} ~~number of~~ ^{number of} ~~analyses~~ ^{analyses} to
confirm the presence of 2,3,7,8-TCDD.

Dependent upon the facility availability of ^{facilities} it
 might also be possible to administer daily
 doses of ^{14}C -TCDD to monitor excretion
 and body burden kinetics. Such an ~~idea~~
~~approach~~ would substitute radioactivity analyses
 for ^{14}C -TCDD in ~~the~~ urine and feces for ^{14}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~~ reducing ~~in~~ the initial
 number of complex chemical analyses which
 should ~~and~~ reduce the cost of conducting

that studies.

Hopefully these suggestions will be
useful in establishing a sound experimental
program. This would welcome the opportunity
to discuss this with you, ^{with} others whom
~~that~~ you might suggest.

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