

Some Comments on Low Dose Effects of TCDD on Brain Development and Behavior

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Thank you, Mr. Chairmen. May I have the first figure?

Dear Folks, it is my great honor to give some comments to Dr. Weiss's work, since Dr. Weiss is my ex-teacher when I was a graduate student at the university of Rochester 20 some years ago. I really hope that he would get over very soon.

At this opportunity, I will focus my comments upon the following two aspects.

The first aspect is behavioral teratological findings with a special reference to a low dose TCDD. The second aspect is how we apply these data to dioxin risk assessment in the real world.

The study that has been performed in Dr. Weiss's laboratory strongly suggest the possibility that not only hypothalamic-pituitary-gonadal axis but also advance brain function might be affected by the perinatal exposure to TCDD.

It is very interesting to note that the scheduled-controlled operant behavior such as run opportunities was independent from the estrous cycle. Since Ms. Hojo mentioned that this type of behavior is often observed in a female-specific manner, it would be interesting to study how this particular TCDD exposure affects male rats.

Since Holtzman rats are known to be very sensitive to TCDD partly due to the high affinity of aryl hydrocarbon receptor, it would be worth looking other animal species, another strains of rats as well as AhR dependency by utilizing AhR KO mice.

Very recently, Dr. Takeyama in my research team has reported some molecular-based evidence that may support Dr. Weiss's behavioral teratological data as shown in the next figure.

We administered pregnant Holtzman rats a low-dose of TCDD on gestational day 15, and determined mRNA of NR2A and NR2B types of glutamate-NMDA type receptor in the neocortex and hippocampus on post-natal day 5 and 49 by the use of competitive RT-PCR. We found that NR2B subunit mRNA was decreased on PND49 in a dose-dependent manner by as low as 200 ng/kg of TCDD, the dose of which is very close to that of Dr. Weiss's experiment.

Since NMDA receptor is thought to be involved in the memory function we think that this observation is highly important in terms of representing an very early change in the brain function on a molecular basis.

Finally, I would like to make a general comment on the aspect of risk assessment of dioxin by referring Dr. Weiss's data as an example.

Ms. Hojo presented data as bench-mark dose curve fitting. But I would draw your attention that TDI values not only for dioxin but also for other chemicals have been derived from conventional NOAEL approach. For example, in case you use ED01 of approximately 10 ng/kg of body burden, your estimated TDI value becomes approximately 0.5 pg/kg/day.

So, before applying the BMD curve fitting, I would suggest that the method should be validated from various aspects in terms of number of data points, shape of curve. For example, the data published in the journal of Environmental Health Perspective show U-shape, not linear.

I think that it is worth studying what and how we develop and adopt appropriate modeling for curve fit, but I would say that it is still premature to apply them in the real world.

The other important point is that most of the researchers are interested in the mechanism of toxicity. So, we often do not pay attention how much TCDD is accumulated in the organs or tissues. So, it would be extremely important, even mandatory to determine TCDD concentrations in animal studies, the data of which are used for risk assessment. For validation it would be most appropriate if we can compare the TCDD concentrations in various organs and the injection solution ideally among different laboratories.

I agree that the finding from Dr. Weiss's laboratory is one of the lowest TCDD doses that result in behavioral effects. Our data on the decrease in gene expression of androgen receptor in the prostate of rat offspring is currently the lowest TCDD concentration that was recently adopted by JECFA, a joint expert committee of WHO and FAO, to derive a new standard. But I would think that we should be careful enough to derive the LOAEL or NOAEL not from a single report, but from a combination of various dataset in terms of various endpoints.

Finally, I would say that Ms. Hojo's presentation today is extremely important in terms of providing experimental support that may be relevant to subtle behavioral and cognitive alterations reported by Dutch and other epi studies.

Thank you for your attention.