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**COMMITTEE OF EXPERTS ON THE TRANSPORT OF
DANGEROUS GOODS AND ON THE GLOBALLY
HARMONIZED SYSTEM OF CLASSIFICATION
AND LABELLING OF CHEMICALS**

Sub-Committee of Experts on the Globally
Harmonized System of Classification
and Labelling of Chemicals

Ninth session, 11-13 July 2005
Item 2 (b) (iv) of the provisional agenda

**UPDATING OF THE GLOBALLY HARMONIZED SYSTEM OF CLASSIFICATION AND
LABELLING OF CHEMICALS (GHS)**

Health hazards

Toxic to reproduction substances

Scientific issue on reproductive toxicity potency

Transmitted by the Organization for Economic Co-operation and Development (OECD)

1. Reproductive toxicity combines two or more different types of effects involving sexual function and fertility as well as development of the offspring. These effects are exceedingly complex and overlapping. Effects may include significant but subtle hormonal changes to severe effects of sexual or gamete producing organs. These may be behavioural changes or changes to the integrity of reproductive systems. Similarly, the developmental effects in the offspring range from delay in ossification to changes that may affect behaviour of the adult pup or changes that may lead to mortality of the foetus.
2. Some effects may be observed in a sub-chronic study while others may take a two generation study to manifest. It is also clear from systematic animal research and epidemiological studies that significant and serious effects, especially developmental toxicity, can be caused by a single exposure or a narrow exposure window to a chemical.
3. Typically, the effects vary greatly in severity and/or causative dose level from one species to another; for example, thalidomide manifests skeletal abnormalities with a range of doses across species of at least 3 orders of magnitude. It is well known that there is no orderly systematic way of predicting potency of a particular effect from one species to another. Moreover, some effects are manifest at low doses, some at high doses in one species and the order can be reversed in another species. Among other

things, this complexity has led to the generalized regulatory requirement that developmental toxicity be tested in two species, rather than one, so as to be sure not to miss the potential for developmental toxicity (for drugs and pesticides, among others).

4. The many considerations needed to compare relative risk of two chemicals for reproductive effects are so complex that this can only be considered as viable for classification on a case-by-case basis. This is possible within the GHS system as currently agreed. For example, competent authorities may wish to make certain exceptions to the general rule of 0.1%-3% for inclusion of reproductive toxicants in mixtures. The GHS allows for this at paragraph 1.3.3.2.1.

5. For such a complex and highly variable endpoint, the use of dose cut-off values as a manifestation of "relative potency" is not recommended at the present stage of scientific knowledge. The fact that the effects in the endpoint can be observed in such a highly diverse set of tests or observations works against the use of cut-off levels such as those applied in TOST or acute lethality, where comparisons are made of the same types of toxic effects, in tests of the same or closely similar duration.

6. Additional information useful for increasing knowledge on reproductive toxicity potency would include guidelines, parameters, criteria reflecting consensus of expert groups with respect to potency, or list of chemicals with ranking and idea of distribution. Not only NOAELs or LOAELs for developmental toxicity and for effects on fertility are needed. Depending on the effects that would need to be considered, several NOAELs/LOAELs may have to be considered as well as other parameters such as effects variability from one species to another.

7. The information available at the ILSI does not focus on reproduction studies and would not be very useful for the OECD work on HCL. No information from WHO/IPCS is currently available on reproductive toxicity potency.

Conclusions

8. Available scientific knowledge on the complex issue of reproductive toxicity potency does not allow a general revision of the classification criteria, and only a case-by-case approach, on the basis of GHS Section 1.3.3.2 is possible. None of the identified possible source of additional information (ILSI and IPCS) can currently provide additional information on reproductive toxicity potency.
