JSTP Comments on European Food Safety Authority (EFSA) Draft Guidance on 90-Day Rodent Toxicity Studies

The Japanese Society of Toxicologic Pathology (JSTP) appreciates the opportunity to give comments on the draft guidance.

The majority of the JSTP members are actively contributing as toxicologic pathologists to the development and/or risk assessment of all types of chemicals including new drugs, pesticides, food additives and environmental chemicals.

The JSTP has been promoting the increase in the number of highly qualified toxicologic pathologists to contribute the development and/or risk assessment of chemicals and has now more than 300 qualified pathologists (diplomates) certified by the JSTP board certification system. The JSTP also provide continuing education courses including histopathology slide conference annually to not only young pathologists but also diplomates to improve their quality as a pathologist..

Our comments are focused on ‘completely randomized design of histopathological examinations’, and mainly addressed to the following two paragraphs in the EFSA draft guidance.

Section 5.2 Lines 505 to 510
Section Appendix 1, Section 4.1 Lines 1107 to 1111

Comments:

In the risk assessment of chemicals, the mission of toxicologic pathologists is to detect definitive histopathological evidence of chemical toxicities accurately.

In chemical toxicity studies, histopathological examinations are primarily based on qualitative analyses by pathologists and are fundamentally different from quantitative analyses of measurable parameters such as body weights, food consumption, hematology, or blood biochemistry. Thus, it is important for pathologists to detect treatment-related toxic changes beyond normal variations qualitatively..

Since toxicologic pathologists analyze many tissues and/or organs of whole body for each animal, it should be recognized that whole body analysis is always accompanied by wide range variations in various tissues and is influenced by many factors including fate of animals and tissue preparation process. Therefore, toxicologic pathologists need the relevant information as much as possible from the toxicological studies conducted.

To keep accuracy and consistency of histopathological analysis, toxicologic pathologists need information on treatment groups (control or treated) and summarized group mean and individual data available including clinical signs, body weights, hematology, blood biochemistry, or urinalysis obtained from the conducted toxicity studies, especially in the initial histopathological review. The information gives confidence in their pathological diagnoses.

In blinded/masked analysis, pathologists are very concerned about an increase in the risk of overlooking treatment-related changes. On the contrary, overdiagnosis resulting from being too sensitive for minimum changes might result in confusion of toxicity identification.
A 90-day toxicity study is very important to clarify toxicological profiles of the test substance.

In our conclusion, histopathological examinations in a blinded/masked fashion without awareness of treatment groups or relevant information may increase the risk of overlooking early or subtle toxic changes, leading to loss of accuracy of analysis which might be more risky than that caused by conscious bias.

Based on the comments described above, the JSTP strongly requests the draft guidance be revised to indicate that toxicologic pathologists should analyze under awareness of treatment groups and other relevant information. Regarding the methodology of pathological examinations in toxicity studies, the JSTP basically endorses the STP position paper (Crissman et al. Best Practices Guideline: Toxicologic Histopathology. *Toxicologic Pathology*, 32:126–131, 2004).

Note: The JSTP also understands the importance of objectivity and transparency in histopathology. Blinded histopathological examinations may increase the objectivity and transparency, whereas it also increases the risk of overlooking treatment-related changes which results in loss of accuracy. Although the transparency, objectivity and accuracy are all important for histopathological evaluation, the JSTP would like to give the priority to the accuracy over others for risk assessement. Further discussion is required to reach consensus among the concerned communities (e.g. regulatory agencies, industry, contract research organization, and academia). The best balance to resolve the above issues should be sought in the near future.