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Continuing harmonization of terminology and innovations for methodologies in developmental toxicology: Report of the 8th Berlin Workshop on Developmental Toxicity, 14–16 May 2014

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ABSTRACT

This article is a report of the 8th Berlin Workshop on Developmental Toxicity held in May 2014. The main aim of the workshop was the continuing harmonization of terminology and innovations for methodologies used in the assessment of embryo- and fetotoxic findings. The following main topics were discussed: harmonized categorization of external, skeletal, visceral and materno-fetal findings into malformations, variations and grey zone anomalies, aspects of developmental anomalies in humans and laboratory animals, and innovations for new methodologies in developmental toxicology. The application of Version 2 terminology in the *DevTox* database was considered as a useful improvement in the categorization of developmental anomalies. Participants concluded that initiation of a project for comparative assessments of developmental anomalies in humans and laboratory animals could support regulatory risk assessment and university-based training. Improvement of new methodological approaches for alternatives to animal testing should be triggered for a better understanding of developmental outcomes.

1. Introduction

The scientific and administrative needs for a harmonized terminology for classification of anomalies were the initial motive to launch the series of Berlin Workshops [1–4]. These workshops are part of an international project in the field of harmonization of terminology in developmental toxicology supported by the World health Organization (WHO). The first Workshop in 1995 discussed the uses and misuses of the International Federation of Teratology Societies (IFTS) glossary, which is presented in the publication of the first report [5]. Focus of the previous (7th) Berlin Workshop in 2011 was placed on the continuing challenges regarding descriptive terminology and classification of fetal observations,

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with particular reference to knowledge on the postnatal fate of fetal anomalies and to the application of Version 2 terminology of developmental abnormalities in common laboratory mammals [6] to non-routinely used species [7]. Version 2 included numerous revised terms, added many new terms, and introduced a new class of findings (maternal–fetal abnormalities).

As a further result of the 2011 Berlin Workshop, the "*DevTox* database" (www.devtox.org) [8] was adapted to the Version 2 terminology, and all files controlling the web site structure were updated. Where possible, images for the new findings were added and the suitability of the updated terminology for the inclusion of new uncommon species (primates, birds, dogs, Guinea pigs) was evaluated. After successful completion of the update, the website was re-launched in August 2012 to form the basis for scientific discussion of the new findings [8]. A total of 1742 observations were available, 911 of which were introduced and 831 renamed, and 66 outdated observations were deleted. However, none of the new terms were categorized yet as malformations, variations or grey zone anomalies. Based on the former IFTS terminology results of several surveys on rat fetal skeletal terminology [3] and on rat fetal external and visceral terminology [4] were discussed during the previous Berlin Workshops and the agreed classifications were published. Therefore, the 7th Workshop in 2011 recommended that according to the same methodology published for the earlier surveys [3,4] a new survey should be conducted on fetal observations using Version 2 terminology, to categorize the new terms as malformations, variations, or grey zone anomalies. The new survey of the categorization of new terms in Version 2 nomenclature was initiated in November 2013. During the 2014 workshop the survey responses were presented and discussed with the invited experts and the translation of the "*DevTox* database" into Chinese language was proposed.

Summing up the discussions held during the last workshops on the harmonization of the terminology used in the assessment of findings in developmental toxicology, the same issues repeatedly emerged:

1. More systematic information is needed for categorization of anomalies and their causes,
2. Comparable information is needed in animals and humans.

These requirements stimulated the approach to address the content from different perspectives during 8th Berlin Workshop on DevTox Terminology: harmonized categorization of external, skeletal, visceral and maternal–fetal findings into malformations, variations and grey zone anomalies, aspects of developmental anomalies in humans and laboratory animals, and innovations for alternatives and new methodologies in developmental toxicology.

2. Categorization of Version 2 terminology

2.1. Survey of new terms in Version 2 nomenclatures

The methodology utilized in the survey performed in 2012 is described in detail in previous publications [3,4].

In 2012, the Version 2 terminology of developmental abnormalities [6] was used to update the *Dev*Tox Nomenclature Website (www.devtox.org). This resulted in deletion of a few terms, renaming of most of the old terms and addition of new terms, namely 54 external, 583 skeletal, 280 soft tissue and 17 maternal–fetal terms. While the previous categorizations as malformation, variation or grey zone anomalies could be preserved in the renamed terms, all new terms were implicitly devoid of such categorization. It was noted that Version 2 [6] was intended to provide standardized terminology that could be used to describe all or most potential types of morphological observations. Therefore, a survey was conducted in 2013, asking experts in the field of developmental toxicology for their recommendations on categorization of the new terms. Spreadsheets containing all previously unclassified terms were sent to the experts with the request that they indicate the codes M (malformation), V (variation), U (unknown) or G (grey zone) for each term. As a result of the survey, 20 questionnaires were completed by a sufficient range of expert opinions from single experts or working groups by the major practitioners of developmental toxicology from North and South America, Japan and Europe. After minor adjustments, e.g., interpreting respondent entries of "M or V?" or "M, V" as equivalent to "G", the individual counts of the different codes were tallied for each term. These showed that malformations and variations could be identified by individuals in all four categories of findings.

To categorize the individual observations, an index of agreement (IA %) was calculated according to the following formula, which was derived and utilised at the 4th Berlin Workshop: $(M - V)/(M + V + G) \times 100$. Non-responses and the response "unknown" were not considered in this evaluation. The index varied from +100% for complete consensus on malformations to −100% for complete consensus on variations, and good agreement was indicated by values $\geq$75% and $\leq$−75% [3]. Taking these limits as cut-off criteria, 18 external, 110 skeletal and 68 soft tissue terms were identified as malformations and 129 skeletal and 1 soft tissue terms as variations. The remaining 36 external, 344 skeletal and 211 soft tissue terms as well as all 17 maternal–fetal terms were regarded grey zone, although some of these terms have an index of agreement near the selected criteria. The results for the terms added according to restricted species availability were in good concordance with those obtained previously. More detailed results of the survey responses are published under www.devtox.org

2.2. Categorization of external anomalies

Approximately one third of the external anomalies were categorized as malformations by survey responders. Workshop participants highly agreed on fetal observations with terms such as "absent", "fused", "misshapen", and "malpositioned" to be categorized as a malformation. The majority of the survey respondents categorized "papillae fused" as a malformation; however, the anatomical site and the observation "fused" were discussed and debated. Since papillae [dermal structure around the snout and origin of whiskers outgrowth] were never seen in a fused position by any of the workshop participants, the general question arose why findings should be categorized when they have never been observed. On the other hand, Version 2 [6] was intended to provide standardized terminology that could be used to describe all or most potential types of morphological observations.

The term "misshapen", defined simply as "abnormally shaped" in Version 2 [6], implies that an anatomical structure is malformed, as concluded in previous Berlin Workshops. However, it is recognized that this term might also be used for a variation, in case no alternative term is available. This approach was confirmed by some workshop participants who indicated that they use "slightly misshapen" for a finding that they categorize as a variation.

Many findings were categorized as "grey zone anomalies" (G), that is, findings which cannot be categorized in either "M" or "V" based on the available study information. This was also the case for the terms "large" and "small" (Table 1). The recommendation that "grey zone" anomalies should be better described was already concluded in a previous Berlin workshop [2]. The main reasons for choosing the category "grey zone" anomaly were: imprecise terms, insufficient knowledge on postnatal consequences, and the possibility of observing a range of severity that might be decisive for the categorization of either a malformation or variation.