25 years DevTox Workshops: scientific improvements

Where we were and where we are now

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Introduction

Up until the 1990s:

- **Each lab conducting studies on developmental toxicity had its own „internal“ nomenclature for different findings**
- **As a result: no consistent terminology across labs available**
- **Instead: Mix of terms e.g. anomaly versus abnormality**
- **Mix between description of findings and classification**
- **Mix between diagnoses from human medicine and description of findings (external only)**

Introduction

Further problems:

- **Medical terms were not suitable for lab technicians**
- **The term „teratogen“ was applied to any anomaly.**
- **No pictures available therefore no clarification of findings between different labs**

⇨ risk assessment of substances difficult due to lack of objective comparison

Introduction

- On United Nations Conference on Environment and Development in Rio (1992) international harmonisation in science was requested
- In parallel national scientific groups working in devtox already aimed for harmonisation within their countries
- Working group from International Federation of Teratology Societies (IFTS) Committee on International Harmonization of Nomenclature in Developmental Toxicology also worked on international harmonization of terms
- In 1995 Federal Institute for Health Protection of Consumers and Veterinary Medicine (BgVV) and the Free University of Berlin began to harmonize /standardize the devtox terminology used by IFTS and the International Programme on Chemical Safety (IPCS).
- Meetings of international nomenclature committees

„FIRST Berlin-Workshop on Developmental Toxicology“

Result: Wise et al. (1997) Terminology Version 1

Academia, regulatory agencies and industry from US, UK, F, GER, HUN, Japan

TERATOLOGY 55:249–292 (1997)

Terminology of Developmental Abnormalities in Common Laboratory Mammals (Version 1)

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[12]*U.S. Environmental Protection Agency, NCEA, Washington, DC, 20460; currently on detail to the Food and Drug Administration, NCTR, Rockville, Maryland, 20857*
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[23]*Food and Drug Administration Standardized Nomenclature Program*

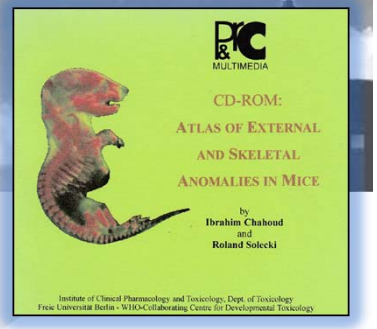
Wise et al.: No classification of anomalies, glossary of terms only

„The purpose of this effort is to provide a common vocabulary that will reduce confusion and ambiguity in the description of developmental effects, particularly in submissions to regulatory agencies worldwide. The glossary contains a primary term or phrase, a definition of the abnormality, and notes, where appropriate."

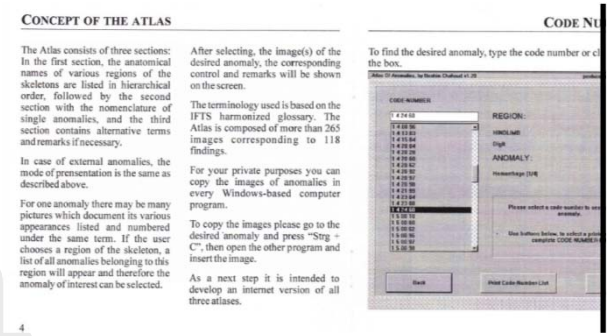
"A ranking or classification of terms into categories, such as malformation and variation, does not appear in the glossary since a given observation may be a malformation in one species but a variation in another species, or the classification may change depending on the gestational day of examination. In addition, there is no consensus at present as to which classification scheme is most relevant."

Wise et al. (1997) *Teratology*, 55:249–292

Atlas of External and Skeletal Anomalies



- **In parallel project for atlases was initiated**
- **Approx. 2000 images provided by Institute of Clinical Pharmacology and Toxicology, Department of Toxicology, FU Berlin, Germany (~ 80% of all pictures)**
- **From academic basic research with teratogenic (reference) substances** (e.g. FUDR, Gancyclovir, ARAC, Hydoxyurea)
- **Initially using „internal“ nomenclature**
- **Digitalisation and attribution to code numbers and version 1 terminology**
- **Rat & Rabbit 1997, Mouse 2001**
- **Subsequent integration into DevTox.org website**


CONCEPT OF THE ATLAS

The Atlas consists of three sections: In the first section, the anatomical names of various regions of the skeletons are listed in hierarchical order, followed by the second section with the nomenclature of single anomalies, and the third section contains alternative terms and remarks if necessary.

In case of external anomalies, the mode of prensentation is the same as described above.

For one anomaly there may be many pictures which document its various appearances listed and numbered under the same term. If the user chooses a region of the skeleton, a list of all anomalies belonging to this region will appear and therefore the anomaly of interest can be selected.

After selecting, the image(s) of the desired anomaly, the corresponding control and remarks will be shown on the screen.

The terminology used is based on the IFTS harmonized glossary. The Atlas is composed of more than 265 images corresponding to 118 findings.

For your private purposes you can copy the images of anomalies in every Windows-based computer program.

To copy the images please go to the desired anomaly and press "Strg + C", then open the other program and insert the image.

As a next step it is intended to develop an internet version of all three atlases.

4

CODE NU

To find the desired anomaly, type the code number or cl
the box.

REGION:

ANOMALY:

SECOND WORKSHOP ON THE TERMINOLOGY IN DEVELOPMENTAL TOXICOLOGY BERLIN, 27–28 AUGUST 1998

- Experts from research institutions, regulatory agencies and industry
- The absence of harmonization of terminology is no longer acceptable for regulatory purposes.
- Harmonization of terminology is necessary for classification of structural anomalies.
- **Participants put forward a scheme of classification for fetal abnormalities that consists of only two categories: “malformation and variation.”**

Chahoud et al. (1999) *Reproductive Toxicology*, 13 (1): 77–82

Preparations for Third Berlin Workshop

- **Survey for classification of skeletal anomalies was sent out**
- **Classification should be conducted within the definitions agreed upon at 2nd workshop**
- **Additional categories U** (Can´t decide) **and N** (Term not known/not used)
- **Use of Version 1 terminology**
- **Approx. 25 labs contributed internationally, 13 experts responded to survey**
- **Results discussed in steering committee**
- **Index of agreement (IA) was introduced by Francisco Paumgartten:**

$$IA = [(M - V)/(M + V + U)] \times 100$$

(maximum scores for agreement were + 100 for malformation or - 100 for variation)

THIRD WORKSHOP ON THE TERMINOLOGY IN DEVELOPMENTAL TOXICOLOGY BERLIN, 14-16 SEPTEMBER 2000

- **Results of a survey on the classification of skeletal anomalies were discussed**

- **Good IA: > 75 no discussion necessary**
- **Poor IA: < 25 discussion of anomalies necessary**

- Main focus on terms for which there was disagreement and/or uncertainties

- Pictures provided by the participants for the illustration of “grey zone” anomalies as basis for detailed discussions

- **Reasons for low agreement:** imprecise terms, insufficient knowledge on postnatal consequences, theoretical terms that are unlikely to occur in isolation

- **Range of severity might be decisive for the classification of either a malformation or variation.**

Solecki et al. (2001) *Reproductive Toxicology*, 15: 713–721

FOURTH WORKSHOP ON THE TERMINOLOGY IN DEVELOPMENTAL TOXICOLOGY BERLIN, 18-20 April 2002

- **Results of a survey on the classification of external and visceral anomalies were discussed (1997 IFTS glossary)**
- **High IA that most of the external anomalies (>66%) should be classified as malformations**
- **Most of the visceral findings had low agreement indices for several reasons** (only rarely seen, tends to be species specific, availability of appropriate historical control data, description of grading and severity, irreversibility unclear)
- **Classification of some visceral anomalies as malformation or variation will remain vague as the decision must be made on a case-by-case**
- **The term "unclassified" was agreed upon ("Not malformation")**

Solecki et al. (2003) *Reproductive Toxicology* 17:625–637

FIFTH WORKSHOP ON THE TERMINOLOGY IN DEVELOPMENTAL TOXICOLOGY BERLIN, 27–29 October 2005

- **Fifth workshop: discussion of a draft international proposal for updating the glossary of descriptive terms for fetal abnormalities put forward by Wise et al. 1997**

- **Previous coordination via e-mails, telephone conferences, meeting**

- **Participants were asked to classify the new external, visceral and skeletal observations included within this draft of the new version 2 according to the scheme (M, V, U) agreed upon at previous Berlin workshops**

Paumgartten et al. (2009) *Reproductive Toxicology 27*:8–13

SIXTH WORKSHOP ON THE TERMINOLOGY IN DEVELOPMENTAL TOXICOLOGY BERLIN, 25–27 October 2007

- **Focus on the causes of uncertainty and low agreement regarding classification of some fetal observations as M or V**

- **Main reasons:** Imprecise anatomical terms, observation terms that are too broad, lack of information on severity and the use of different terms for the same change or different severities of the same change, insufficient knowledge of postnatal consequences

- **Severity grading recommended for reduction of misclassifications.**

- **A better knowledge of the adversity and postnatal consequences of fetal observations was considered as key issue**

Paumgartten et al. (2009) *Reproductive Toxicology 27*:8–13

Terminology of Developmental Abnormalities in Common Laboratory Mammals (Version 2)

Makris et al. (2009): Terminology Version 2

Result of international collaboration among interested organizations, individual experts and the outcomes of several workshops.

Birth Defects Research (Part B) 86:227–327 (2009)

Review Article

Terminology of Developmental Abnormalities in Common Laboratory Mammals (Version 2)

Susan L. Makris,[1*] Howard M. Solomon,[2] Ruth Clark,[3] Kohei Shiota,[4] Stephane Barbellion,[5] Jochen Buschmann,[6] Makoto Ema,[7] Michio Fujiwara,[8] Konstanze Grote,[9] Keith P. Hazelden,[10] Kok Wah Hew,[11] Masao Horimoto,[12] Yojiro Ooshima,[13] Meg Parkinson,[14] and L. David Wise[15]

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Terminology of Developmental Abnormalities in Common Laboratory Mammals (Version 2)

- **Improvements and enhancements to content and organization of terminology**
- **Classification into M or V remains unaddressed, as focus of document is descriptive terminology**
- **Introduction of separate table for 'Maternal-Fetal Abnormalities**
- **Several appendices with additional information** (Common Descriptive Terminology Used More Than Once, Syndromes and Combining Terms, Nomenclature–Alternative Terms, Structural Differences–Rat, Mouse and Rabbit, Common skeletal foramina and Processes)

Makris et al. (2009):

***Reprod Toxicol* 28(3):371-434**
***Birth Defects Research* (Part B) 86:227–327**
***Congenit Anom* 49(3):123-246**

SEVENTH WORKSHOP ON THE TERMINOLOGY IN DEVELOPMENTAL TOXICOLOGY BERLIN, 04-06 MAY 2011

- **Focus on knowledge on postnatal fate of anomalies**
- **Use of Version 2 terminology for maternal–fetal observations and non-routinely used species,**
- **Reclassification of "grey zone" anomalies**
- **Categorization of fetal observations for human health risk assessment.**
- **DevTox.org website adapted to version 2 terminology**

Topics for the next Workshop:
grouping of fetal observations for reporting and statistical analysis, new survey for classification using version 2 terminology

Solecki et al. (2013) *Reproductive Toxicology* 35: 48– 55

EIGHTH WORKSHOP ON THE TERMINOLOGY IN DEVELOPMENTAL TOXICOLOGY BERLIN, 14-16 MAY 2014

- **New survey for classification was initiated in 2013**
- **Presentation of survey responses for harmonized categorization of external, skeletal, visceral and materno-fetal findings into M, V, or grey zone anomalies**
- **Discussion of aspects of developmental anomalies in humans and laboratory animals** (inclusion of human findings into DevTox.org website)
- **Innovations for new methodologies in developmental toxicology** (MoA, patterns, screening technologies, computational approach, non-mammalian animal models, imaging techniques)
- **The application of Version 2 terminology in the DevTox.org website was considered useful for categorization of developmental anomalies**

Solecki et al. (2015) *Reproductive Toxicology* 57: 140– 146

NINTH WORKSHOP ON THE TERMINOLOGY IN DEVELOPMENTAL TOXICOLOGY BERLIN, 13-14 SEPTEMBER 2018

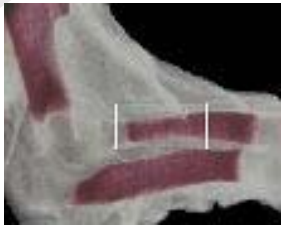
- **The future of *in-vitro* methods for developmental and reproductive toxicology**
- **Potential relevance of alternative species in testing of developmental effects: useful for screening purposes**
- **Risk and hazard assessment of developmental and endocrine effects** (hazard cut-off criteria approach, negligible exposure, low-dose, mixtures)
- **Development of animal-free test strategies and alternatives to animal testing that could provide human-relevant information**
- **Comparative aspects lab animals vs. human considered important**
- **Regular employment of postnatal evaluation of anomalies within other studies** (e.g. extended-one-generation)
- **Chinese version launched on DevTox.org website in 2016**

Solecki et al. (2019) *Reproductive Toxicology* 89: 124–129

Resumé: Where we are now

- **International accepted terminology**
- **Basis for classification**
- **Images for many findings available**

www.devtox.org



- **Many experimental species included** (e.g. quail, primates, guinea pig, minipig)
- **Some images of findings from postnatal studies**
- **DevTox.org website basis for international developmental toxicologists (e.g. Chinese version)**

Resumé- where we are now

- **All achievements by cooperation of academia, regulatory agencies and industry**

- **Application not obligatory, deviations possible if scientific reason and images are provided**

This cooperation has to go on for continous improvement !

Open Questions

- **Severity grading**
- **Postnatal fate of anomalies**
- **Use of imaging techniques for individual follow up of postnatal fate of anomalies**
- **Development of animal-free test strategies**
- **Continous process: reduction of still existing grey zone anomalies**

Many tireless fighters for harmonization of terminology……

TERATOLOGY 55:249–292 (1997)

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ELSEVIER

Reproductive Toxicology
Volume 89, October 2019, Pages 124-129

Update of the DevTox data database for harmonized risk assessment and alternative methodologies in developmental toxicology: Report of the 9th Berlin Workshop on Developmental Toxicity

Roland Solecki [a], Martina Rauch [a], Andrea Gall [a], Jochen Buschmann [b], Rupert Kellner [d], Olena Kucheryavenko [a], Anne Schmitt [a], Nathalie Delrue [e], Weihua Li [f], Jingying Hu [f], Michio Fujiwara [g], Makiko Kuwagata [h], Alberto Mantovani [i], Susan L. Makris [j], Francisco Paumgartten [k], Gilbert Schönfelder [a, c], Steffen Schneider [m], Silvia Vogl [a], Nicole Kleinstreuer [n], Marlon Schneider [a], Frank Schulze [a], Ellen Fritsche [c], Ruth Clark [p], Kohei Shiota [q], Ibrahim Chahoud [r]

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….. with Roland providing ideas, organization and responsibility for BfR support for this important project

Special thanks to Brigitte Woelffel (†)

Thank you for your attention