Retrospective analysis of the terminology harmonisation process during the Berlin workshops

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

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Classification terms in developmental toxicology: need for harmonisation

Report of the second workshop on the terminology in developmental toxicology Berlin 27-28 August 1998

Chahoud et al. *Reproductive Toxicology* (1999)

Outcome of the second workshop

- a scheme of classification for foetal abnormalities
- only two categories: malformation and variation

Outcome of the second workshop

Malformation is a permanent structural change that is likely to adversely affect the survival or health of the species under investigation.

Outcome of the second workshop

Variation is a change that occurs within the normal population under investigation and is unlikely to adversely affect survival or health.

This might include a delay in growth or morphogenesis that has otherwise followed a normal pattern of development.

Malformation ⟹ Permanent **and** harmful anomalies

Reversible ⟺ Permanent

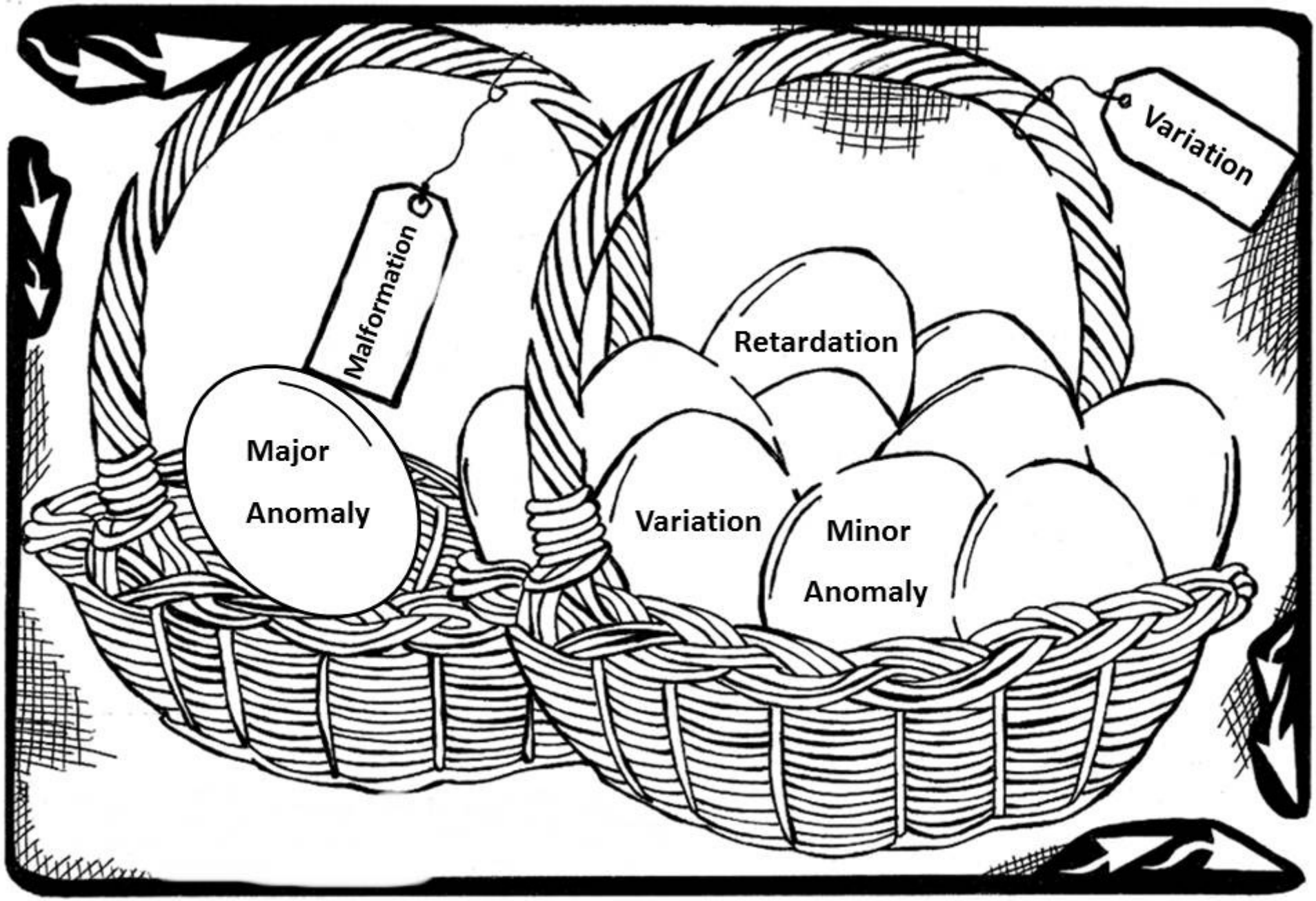
Not harmful ⟺ Harmful

Table 1. Proposal of a classificatory scheme for structural abnormalities detected at term [Based on mutually-exclusive categories]

Characteristic	Reversibility	Spontaneous incidence	Harmfulness
Retardation	+	+	−/+
Variation	−	+	−
Malformation			
Minor	−	+	−
Major	−	−	+

Variation

Malformation


Malformation
Major
Anomaly
Retardation
Variation
Variation
Minor
Anomaly

Harmonisation of rat fetal skeletal terminology and classification.

Report of the third workshop on the terminology in developmental toxicology
Berlin, 14–16 September 2000

Solecki et al. *Reproductive Toxicology* (2001)

Outcome of the third workshop

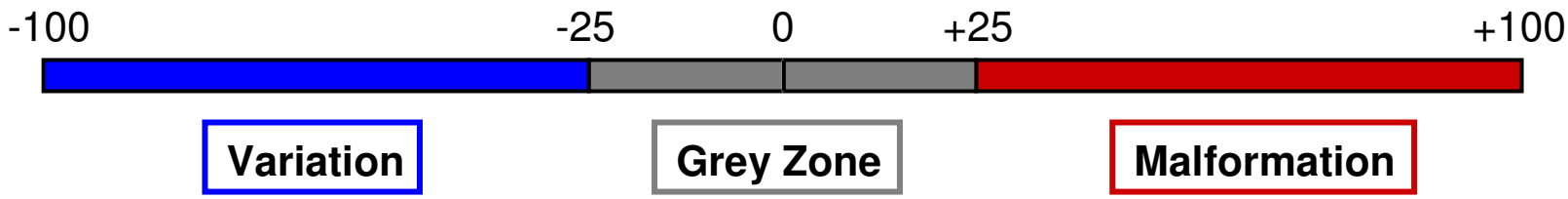
A survey was carried out to test the feasibility of classifying the skeletal abnormalities listed in the IFTS glossary within the definitions agreed to at the second workshop.

Analysis of 3rd workshop survey results

- Index of Agreement (IA):

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

M : Malformation
V : Variation
U : Can't decide



Outcome of the third workshop

In addition to the classification terms *malformation* and *variation,* two further categories were used in the survey:

– *can't decide between malformation and variation*

and

– *term not known/not used in this laboratory*

Outcome of the third workshop

The discussions at the workshop focussed on those terms for which there was disagreement and/or uncertainties and the possible reasons
(“grey zone anomalies ”)

Table 4
Indices of agreement for sternebrae and vertebrae

Bone	Absent	Fused	Malpositioned	Misaligned	Misshapened	Incomplete ossification	Unossified	Small	Hemivertebra	Supernumerary	Hemicentric	Split cartilage	Unilateral cartilage	Bipartite ossification	Dumbbell
Sternebra	84.6	15.4	76.9	−50.0	−15.4	−84.6	−84.6							−66.7	
Vertebra	100									23.1					
Cervical arch	100	92.3	100	−8.3	61.5	−84.6	−53.8	58.3		61.5					
Cervical Ct.	100	92.3		8.3	7.7	−84.6	−46.2			69.2	27.3	23.1	41.7	−53.8	−58.3
Cerv. Ct. Cart.		75.0													−58.3
Cervical Vert.	100		83.3						83.3	46.2					
Thoracic arch	100	84.6	75.0	7.7	15.4	−84.6	−46.2	38.5		61.5					
Thoracic Ct.	100	84.6		8.3	15.4	−84.6	−53.8			61.5	16.7	23.1	33.3	−53.8	−58.3
Thor. Ct. Cart.		69.2													−63.6
Thoracic Vert.	100		66.7						83.3	23.1					
Lumbar arch	100	84.6	83.3	0.0	15.4	−84.6	−46.2	30.8		61.5					
Lumbar Ct.	100	84.6		0.0	0.0	−84.6	−46.2			61.5	36.4	23.1	23.1	−53.8	−58.3
Lumb. Ct. Cart.		83.3													−58.3
Lumbar Vert.	100		83.3						83.3	23.1					
Sacral arch	100	100.0	83.3	−8.3	15.4	−84.6	−46.2	41.7		61.5					
Sacral Ct.	100	84.6		0.0	0.0	−84.6	−46.2			61.5	16.7	33.3	23.1	−53.8	−58.3
Sac. Ct. Cart.		69.2													−58.3
Sacral Vert.	100		83.3						66.7	23.1					
Caudal arch	58.3	41.7	50.0	10.0	18.2	−83.3	−45.5	36.4			0.0			−54.5	
Caudal Ct.	83.3	36.4		0.0	0.0	−81.8	−45.5								−54.5
Caudal Vert.	33.3		36.4						33.3	−36.4					

Ct, centrum; Cerv, cervical; Vert, vertebra; Thor, thoracic; Cart, cartilage; Sac, Sacral.

Table 6
Indices of agreement for cranial bones

Bone	Absent	Fused	Small	Misshapened	Split	Unossified	Hole	Incomplete ossification	Bipartite	Bent
Alisphenoid	100	83.3	66.7	83.3		−11.1	−10.0	−55.6		
Auditory oss.	100	100		100		−33.3				
Basioccipital	100	84.6	53.8	69.2		−30.8	−27.3	−84.6		
Basisphenoid	100	100	66.7	83.3		−25.0	−10.0	−83.3		
Exoccipital	100	100	53.8	69.2		−30.8	−25.0	−84.6		
Frontal	100	50.0	53.8	83.3		−16.7	−18.2	−83.3		
Hyoid	100		33.3	23.1		−63.6		−100		−23.1
Interparietal	100	69.2	53.8	76.9		−41.7	−18.2	−84.6	−76.9	
Lacrimal	100	92.3	40.0	70.0		−40.0		−80.0		
Mandible	100	92.3	76.9	84.6				−84.6		
Maxilla	100	100	76.9	84.6		−7.7		−84.6		
Nasal	100	80.0	69.2	84.6		−7.7	−20.0	−76.9		
Palatine	100	100	61.5	84.6	100	−46.2		−69.2		
Parietal	100	100	53.8	84.6		−15.4	−33.3	−84.6		
Premaxilla	100	100	75.0	83.3		−16.7	−20.0	−83.3		
Presphenoid	100	100	55.6	83.3		−50.0	−71.4	−77.8		
Squamosal	100	100	66.7	69.2		−38.5	−83.3	−84.6		
Supraoccipital	100	100	66.7	83.3		−25.0	−30.0	−83.3	−75.0	
Tympanic ann	100	100	41.7	83.3		−50.0		−83.3		
Vomer	100	100	41.7	75.0		−33.3		−77.8		
Zygomatic	100	100	38.5	84.6		−46.2		−84.6		

Table 5
Rib findings

Finding	Index of agreement
Rib, absent	92.3
Rib, bent	−15.4
Rib, branched	61.5
Rib cartilage, branched	−15.4
Ribs cartilage, fused	−7.7
Rib, cervical	−61.5
Rib, detached	80.0
Rib, discontinuous	−41.7
Rib, fused	84.6
Rib, incomplete ossification	−69.2
Rib, intercostal	72.7
Rib, knobby	−66.7
Rib, malpositioned	100
Rib, misaligned	−9.1
Rib, misshapened	61.5
Ribs, short	38.5
Ribs, thickened	−83.3
Ribs, unossified	−30.8
Ribs, wavy	−76.9
Ribs, supernumerary, full	−84.6
Ribs, supernumerary, short	−100

Outcome of the third workshop

The main reasons for lower agreement were:

- imprecise terms
- insufficient knowledge on postnatal consequences
- theoretical terms that are unlikely to occur in isolation
- the possibility of observing a range of severity that might be decisive for the classification of either a malformation or variation

Harmonisation of rat fetal external and visceral terminology and classification

Report of the fourth workshop on the terminology in developmental toxicology, Berlin, 18–20 April 2002

Solecki et al. *Reproductive Toxicology* (2003)

Outcome of the fourth workshop

Most of the visceral findings had low agreement indices. The response ‘Not known/not used in the laboratory’ was often given.

Difficulties in the classification of an anomaly were
- it is only rarely seen upon fetal examination
- it tends to be species specific.

Outcome of the fourth workshop

The classification of some anomalies as malformation or variation will remain vague as the decision must be made on a case-by-case basis.

Outcome of the fourth workshop

Factors affecting the decision include:

- the availability of appropriate historical control data
- description of the grading and severity
- whether the anomaly occurs in isolation or whether there is a relationship with an abnormal process
- the change represents an irreversible one

Outcome of the fourth workshop

Soft tissue changes were considered likely to be the consequence of functional disorders and thus not strictly developmental anomalies. The possibility to describe a finding as ‘Not Malformation’ (Unclassified) was agreed upon.

As a general conclusion it was emphasized that the observation of a permanent structural change should be considered to be a warning of possible consequences to humans, even when there is no apparent adverse effect on health and survival in adult animals of the species under investigation.

Harmonisation of terminology in developmental toxicology: The quest for a more precise description and a harmonised classification of fetal observations

Report of the fifth and sixth workshop on the terminology in developmental toxicology, Berlin, 2005 and 2007

Paumgartten et al. *Reproductive Toxicology* (2009)

Outcome of the fifth workshop

The fifth Berlin workshop discussions concentrated on a draft proposal for updating the first version of the IFTS International Glossary (“Terminology of Developmental Abnormalities in Common Laboratory Mammals”) published in 1997.

Outcome of the fifth workshop

Participants in the workshop classified the new external, soft tissue and skeletal observations, included within the European proposal, for a new Version of the Terminology of Developmental Abnormalities in Common Laboratory Animals.

Outcome of the sixth workshop

The discussions held at the sixth workshop were focused mainly on two topics:

- lack of precision in descriptive terms
- insufficient knowledge of the postnatal consequences of fetal observations

These were since identified as the major causes for uncertainty and lower agreement among evaluators regarding the classification of "grey zone anomalies".

Outcome of the sixth workshop

Misclassifications and grey zone anomalies could be substantially reduced if

- there were more precise descriptive terms
- harmonized guidance on the use of descriptive terms
- and a more extensive knowledge of the postnatal consequences of fetal observations

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Terminology of developmental abnormalities in common laboratory mammals (version 2)☆,☆☆

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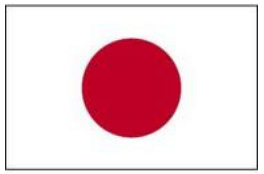

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Terminology of Developmental Abnormalities in Common Laboratory Mammals (Version 2)

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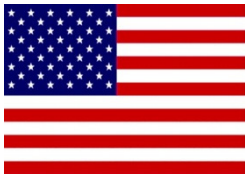

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Review Article

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

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Outcome of the sixth workshop

There is a need for the recording of

- further information as “modifiers”, including the sub-location as part of the structure (anatomical) term

- further description of the nature of the change (in terms of colour, shape, size, position), and, in particular, severity grading,