Follow up activities of the Berlin Workshop with the JTS and ETS

Jochen Buschmann
Consultant in General and Reproductive Toxicology
Hannover
Germany

Malformation vs. Variation

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

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.

Chahoud et al., 1999

Grey Zone Anomalies

In 2009, “grey zone anomalies” were defined as abnormalities that did not fit readily into the categories malformation or variation

Currently, 73 external, 579 skeletal, 370 visceral and all 19 maternal-foetal anomalies are classified as **grey zone**

94 external, 271 skeletal, 157 visceral anomalies are classified as **malformation**

The remaining 173 skeletal anomalies and 6 visceral anomalies are classified as **variation**

JTS Survey

Japanese Teratology Society (JTS) conducted a **survey** limited to **external "grey zone" anomalies**. The questionnaire was completed by 12 companies active in pharmaceutical industries, 6 contracting research labs, 1 company active in chemical industry and 1 environmental research lab

In a first step, **re-categorised anomalies** that were approved by more than 80% in the survey or recommended by the Terminology Committee were selected

In a second step, intense discussion took place in the JTS annual meetings in 2015, 2016 and 2017. As a result, **new possible categorisation** of external findings was suggested by JTS

JTS Survey

Differentiate between uncommon **structural changes** (deviations from normal morphology of the species or strains) and **non-structural abnormalities** (deviations from normal functional without structural changes) in the category “malformation”

Categorisation of 73 external grey zone anomalies:

38 findings were categorised as “malformation”

3 findings as “non-structural abnormality”

1 finding as “malformation” or “non-structural abnormality”

JTS Survey

The remaining 31 findings were considered **to be “not applicable” for foetal examination in rodent/rabbit embryo-foetal development**, because observations were indistinguishable from changes in foetal growth (e.g. large, small, foetus) or easily changeable under physiological condition during examination (e.g. discoloured or pale foetus)

Objectives and goal of the 2019 pre-meeting

European side to get more familiar with the **rationales and applied principles** of the JTS approach.

Try and find a **common position** between ETS and JTS for a potential joint attempt to reduce the number of grey zone anomalies

Presentation of the results of this meeting on the upcoming ETS (JB) and JTS meeting

Get **involved TS** in the process

If possible, apply the **new criteria** in an **update of the DevTox website** in order to further **reduce the number of grey zone anomalies**

Pre-meeting summary

Represenatives of Berlin Workshop (BW) agree with JTS position, according to which some findings can be classified as as “recommended“ , while others, often only theoretically conceivable ones can be considered “non recommended“.

Precondition for BW is that this selection needs to be done based on clear criteria, which by now do not exist. JTS agreed to phrase these as a basis of a discussion with BW. This is the next important, still outstanding step in order to decide the further procedure.

Pre-meeting summary

JTS proposal to classify some external and visceral findings as “non structural anomalies“ is supported by BW, since this is logical analogous approach already applied for skeletal findings, where it is distinguished between structural (S) and ossification (O) findings.

Non structural anomalies as a rule may be classified as variations, although in the end it will come down to a case by case decision.

Pre-meeting summary

There was general agreement that the definition of malformations should be rephrased: ”A permanent structural change with or without an adverse effect on the survival or health of the species under investigation”.

Previous definition: ”A permanent structural change **that is likely to adversely affect the survival or health** of the species under investigation.

This issue should be finally discussed at the 10th Berlin Workshop, which is right now.

Pre-meeting summary

JB presented the current state of the discussion at the 47th Annual Meeting of the European Teratology Society (ETS) September 17-20, 2019 in Cologne in order to find out how ETS role int futur process.

At this workshop, the following main points need to be discussed:

1. Recommended vs. Nonrecommended incl. Criteria
2. Non-structural changes
3. New definition of malformations
4. Future surveys

Objectives and goal of the meeting

Thanks für listening

Now let us start working…