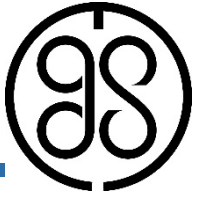




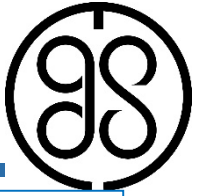
Japanese proposal for update of definitions and re-categorisation of grey zone findings

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Drug Safety Research Labs
Astellas Pharma Inc.



We are grey zone people!
but we hate
the grey zone findings in EFD

Activities to reduce grey zones at JTS and collaboration of Berlin Workshop (BW) and JTS



Questionnaire and discussion were conducted by the JTS Laboratory Animal Term Project (LATP) from 2015 to 2017

Surveyed 20 facilities and 2 experts

Pharmaceutical industries	12
Contract research labs	6
Chemical industry	1
Environmental research lab	1

Decision-making process

1st step Selection of findings that were reclassified abnormally from the results of the questionnaire

2nd step Discussion on experimental animal terminologies during the terminology workshops, which took place during the JTS annual meeting in 2015, 2016, and 2017

Agreement in JTS

- Functional change findings as a new category
- Identify findings not used in fetal examination in rats/rabbits in EFD to distinguish them from grey zone findings
- Refinement of definitions of malformation and variations

JTS activities were reported at the 9th Berlin workshop in 2018

Suggestion from BW: Reconsideration of grey zone-reduction proposals that are acceptable to BW and globally

Pre-BW in Tokyo (July 2019)

Pre-BW meeting was held in Tokyo, where Dr. Solecki, Dr. Buschmann, and JTS discussed grey zone-reduction plans.

JTS LSTP policy on grey zone reduction



The reduction of the grey zone was first discussed at the 4th BW in 2002. However, no further discussion seems to be underway on the following two issues. JTS LSTP focused on these two issues discussed in the 4th BW to develop grey zone reduction plans.

1. Functional changes

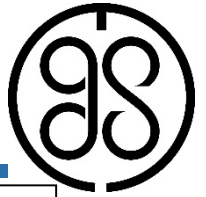
Macroscopic observations like hemorrhagic, pale, discolored, were considered likely to reflect the consequence of a functional disorder and thus not strictly developmental anomalies. A new classification “Not malformation” (unclassified) was proposed. This new category stated that such a findings is not a *sensu stricto* malformation, but due to the functional impairment, it cannot be classified as a variation.

2. Permanent structural changes with unknown effect on health or survival

Observation of permanent structural changes 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. Based on such precautionary principles, an uncommon irreversible abnormal process should be preferably classified as a malformation.”

Harmonization of fetal external and visceral terminology and classification. Report of the 4th Workshop on the Terminology in Developmental Toxicology, Berlin, 18-20 April, 2002
Reproductive toxicology 17(2003) 625-637

Principles for embryo/fetal toxicity evaluation in EFD study



In the assessment of embryo/fetal toxicity due to environmental factors, it is desirable

- ◆ to distinguish between the effects on embryonic developmental processes and the toxicological/ pharmacological effects on the fetus after morphogenesis is completed
- ◆ to ensure that embryonic developmental process disorder should be classified as “malformation” and the delay/reversible or common changes in the species should be classified as "variation".

Embryo/fetal toxicity

Effect on the developmental process

Effect on the fetus after completion of the developmental process

Fetal anomaly

Embryonic lethality

Fetal growth retardation

External, Visceral, or Skeletal

Early death
Late death

Functional changes

- Malformation
- Variation

• **Grey zone**

included?

- **Functional change findings may be included in the grey zone.**
- **The changes should be discriminated from the outputs caused by the effects on the developmental processes**



Findings in the grey zone

The following findings appear frequently in the grey zone

- ◆ Findings that express a change in degree

E.g., large, small, narrow, thick and thin

- ◆ Findings that can be assumed in various cases

E.g., domed, misshapen, high-arched, hyperextension and hyperflexion.



Necessary to wait for the progress in objective measurement and analysis method and for the development of rational judgment criteria.

- ◆ Findings that express functional changes

E.g., discolored, red material , fluid-filled and distended.



These two cases include the findings that can be distinguished from the grey zone regardless of its degree or frequency

- ◆ Findings whose effects on health or survival are unknown but are considered abnormal in the developmental process

E.g., supernumerary, absent, fused and malpositioned.



As a proposal for grey zone reduction



Findings that express functional changes

Establish a new category “Functional change”

Findings whose effects on health or survival are unknown but are considered to be abnormal development

Revise the definition of “malformation” to include all permanent structural changes that are considered abnormal development

Terms that express functional changes



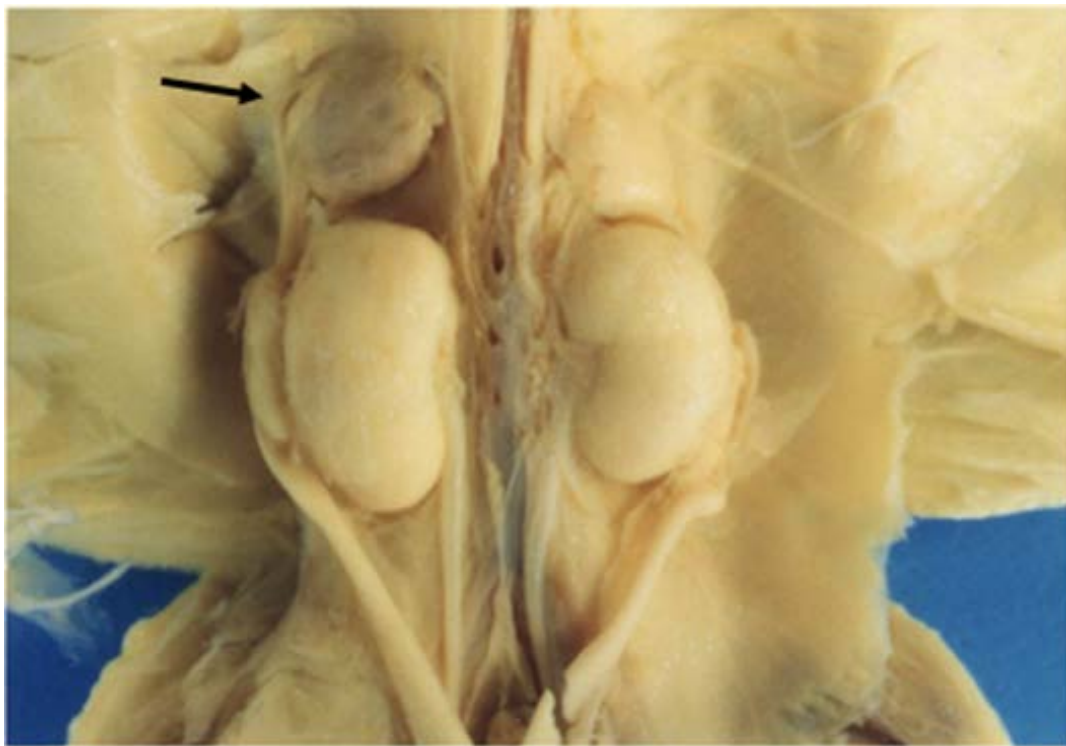
Terms may be included:

- **Discolored**
- **Red material**
- **Edema**
- **Distended**

Example of functional changes



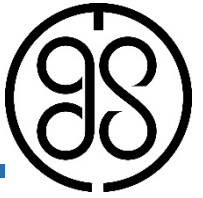
Discolored adrenal gland



Red material in the back



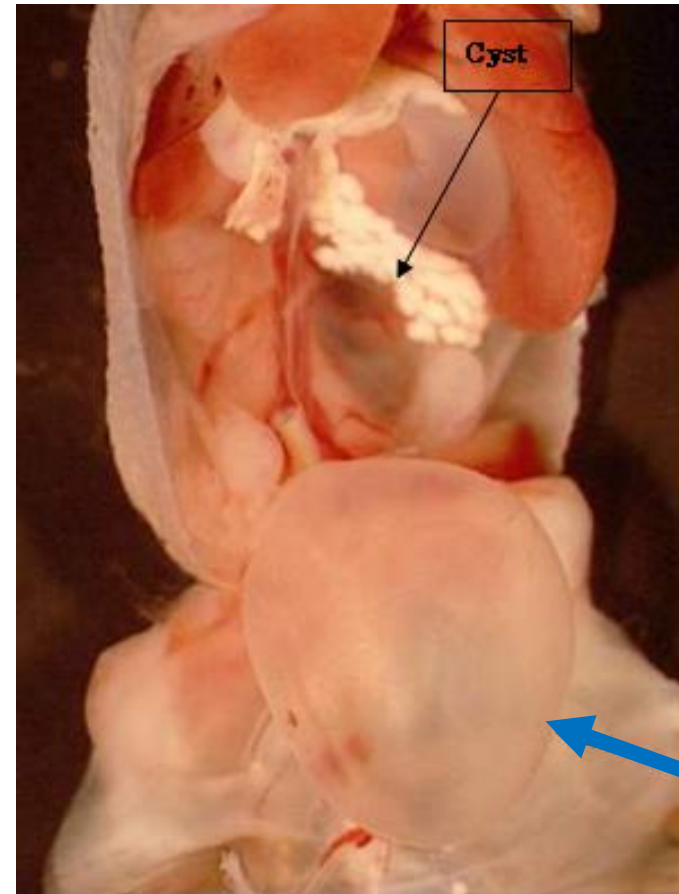
Example of functional changes

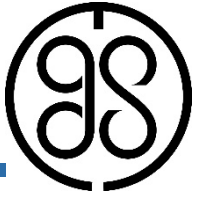


Generalized subcutaneous edema



Distended bladder





Action plan to make functional change a new category

- Agreement of BW members
- Create and confirm the definition of functional change
- Activities for listing candidate findings

JTS LATP proposes “**non-structural functional change**”
as the name of the new category for example

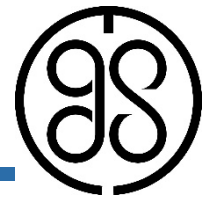
Findings whose effects on health or survival are unknown but are considered abnormal development



Terms may be included:

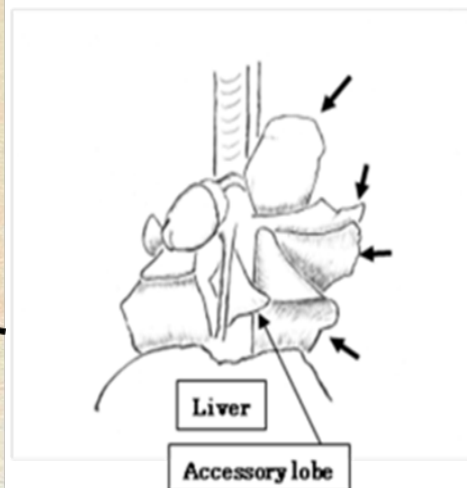
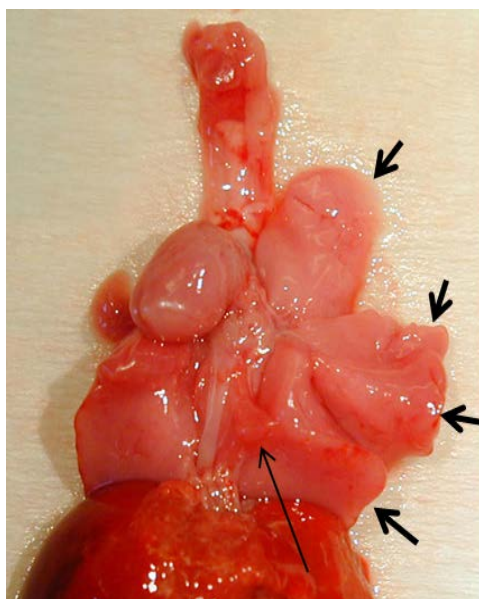
- **Supernumerary**
- **Absent**
- **Fused**
- **Malpositioned**

Examples of findings whose effects on health or survival are unknown but are considered abnormal development

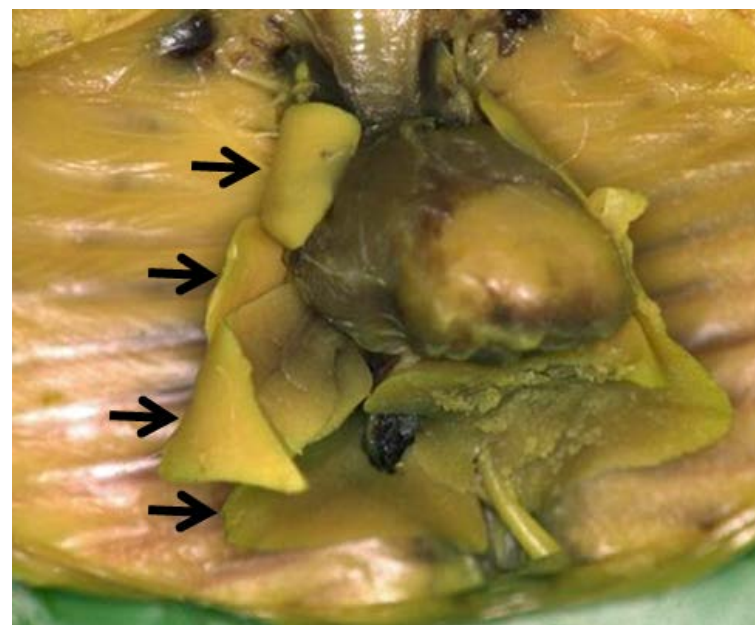


Supernumerary

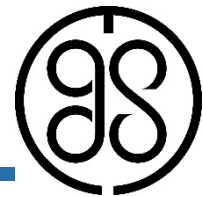
Supernumerary lobes of the lung in rabbit



Supernumerary lobes of the lung in rat



Examples of findings whose effects on health or survival are unknown but are considered abnormal development

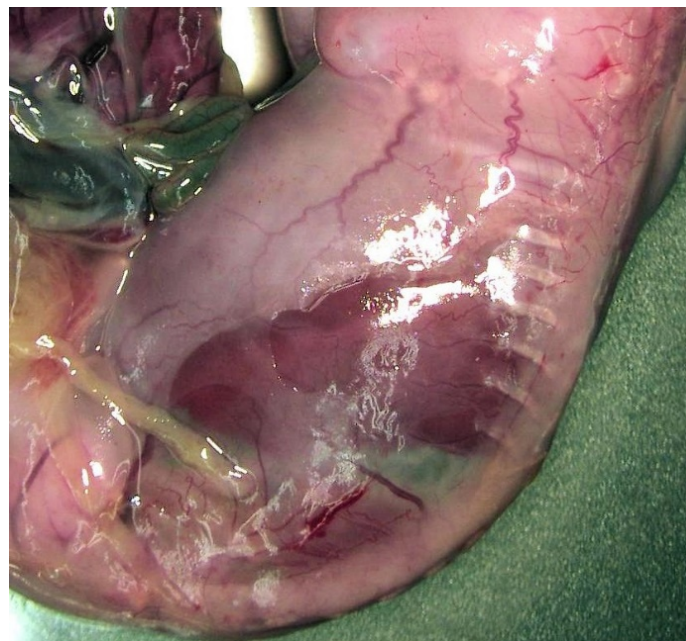


Absent

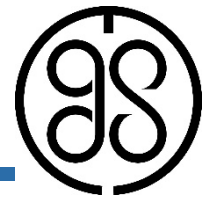
Absent lobe of the liver



Absent skin

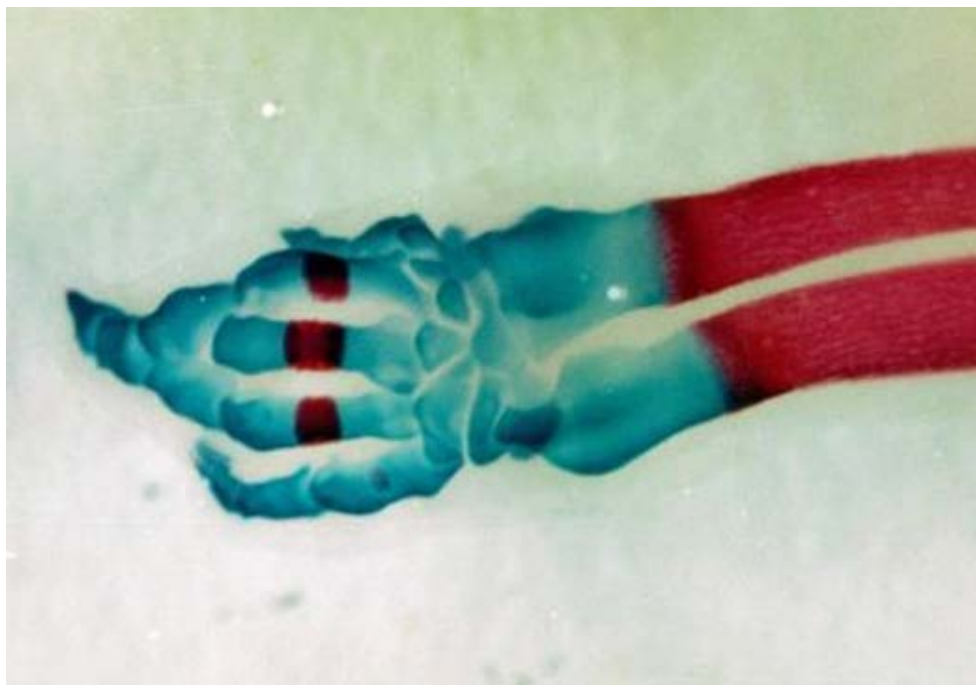


Examples of findings whose effects on health or survival are unknown but are considered abnormal development

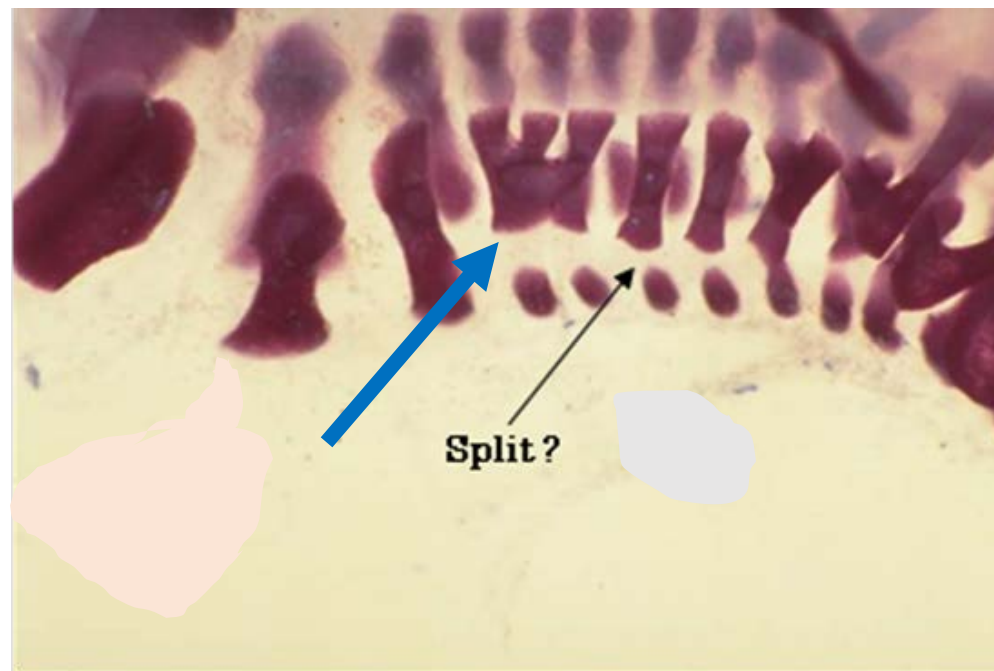


Fused findings

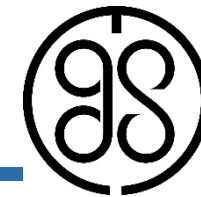
Fused forepaw phalanx



Fused cervical vertebral arches



Examples of findings whose effects on health or survival are unknown but are considered abnormal development

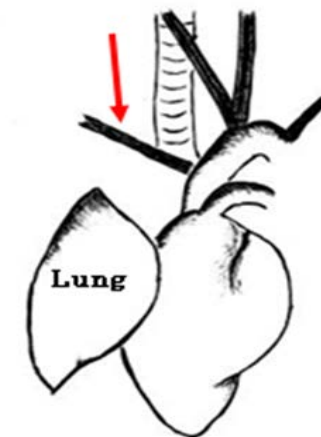
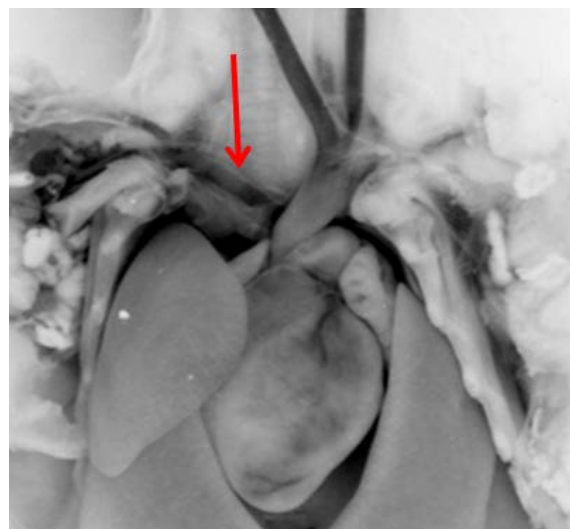


Malposition

Malpositioned left carotid origin and the right subclavian artery



Malpositioned right subclavian artery



Action plan to categorize all permanent structural changes that are considered abnormal development as “Malformations”



- Agreement by BW members with respect to the basic concepts
- Additional description of the definition
- Activities for listing candidate findings

JTS LATP recommends adding a definition regarding the permanent structural changes that are considered abnormal development

Current Definition

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

(Reproductive Toxicology 13, 77-82, 1999)

Additional definition (proposal by JTS)

A permanent structural change resulting from an abnormal developmental process but without evidence or information about the adverse effect.