Overview of the Efforts to Harmonize Terminology of Anomalies in Developmental Toxicology

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Disclosure

The material presented represents the opinion of the author, and does not represent the opinions or views of his employer, Merck & Co., Inc.

Outline

- The Early Years
- Version 1
- Version 2
- “Groupings”
- Future Work

Glossaries in my files

- Health Effects Division, Office of Pesticide Programs, EPA: Standard Evaluation Procedure (11-Oct-1993)
- Glossary by K. Keller and J. Schardein, 07-Aug-1995
- Glossary of Terms (from J. Shardein on 19-Apr-1996)
- Japanese DART Terminology (no date)
- MARTA (1969, 1980, 1987, 1989, 1993)

MARTA (1969)

H.A. Hartman (Sandoz Pharma, Hanover, NJ), Chairman, Committee on Terminology, MARTA

Sample

BONES - GENERAL

ACHONDROPLASIA – disturbance of epiphyseal chondroblastic growth and maturation, causing inadequate enchondfl (*sic*) bone formation and resulting in a peculiar type of dwarfism.

ACNEMIA – 1. atrophy of the calves of the legs;
2. congenital absence of the legs.

AMELIA – absence of a limb or limbs.

BRACHYMETACARPIA – abnormal shortness of the metacarpal bones.

BRACHYMETAPODY – abnormal shortness of some of the metacarpals or metatarsal bones.

MARTA (1989)

Maureen Feuston (Mobil Oil Corp.), Chairwoman, Nomenclature Committee, MARTA

Sample

Hemivertebra	- presence of only one half of a vertebral body
Spina Bifida	- defect in closure of bony spinal canal
a. Spina Bifida Cystica (Aperta)	- spina bifida associated with spinal cord and meninges' protrusion
b. Spina Bifida Occulta	- opening covered by skin; no protrusion of the spinal cord or meninges
Rachischisis	- absence of vertebral arches in limited area (partial rachischisis) or entirely (rachischisis totalis)
Lordosis	- anterior concavity in the curvature of the cervical and lumbar spine as viewed from the side
Scoliosis	- appreciable lateral curvature of the vertebral column

MARTA (1993)

Glossary of Fetal Alterations for Studies of Developmental and Reproductive Toxicology (DART)

Mary Giknis, Joe Mitala, Susan Murray, Howie Solomon, and Dave Wise

"…and will become a starting point for the standardization of nomenclature in the field of developmental toxicity."

MARTA (1993)

Sample

3.7 Appendicular Skeleton

Abasophalangy	Agenesis of the proximal phalanx
Alteration of: Carpus/Tarsus Femur Fibula Humerus Phalanx Metacarpus/Metatarsus Radius Talus/Calcaneous Tibia Ulna	Includes: Agenesis Bowed Displaced Elongated Fused Hypoplastic Incomplete ossification Misshapen Supernumerary Thickened
Amesophalangy	Agenesis of the medial phalanx

Version 1 (1995 - 1997)

Purpose of the Document

To provide a common vocabulary that will reduce confusion and ambiguity in the description of developmental effects, particularly in submissions to regulatory agencies worldwide

Version 1 (1995 - 1997)

USA:

Dave Wise†*‡
Sidney Beck#
Bruce Beyer#
Bob Clark*
Maureen Feuston*
Susan Henwood#
Carole Kimmel†
Pia Lindstrom‡
Judy Petrere#
Howie Solomon*‡
Ray York*

EU:

Diana Beltrame† + Italian wg
Ibrahim Chahoud†
Ruth Clark† + UK wg
Alice Druga†
Pierre Guittin† + French wg
Tony Palmer†

Japan:

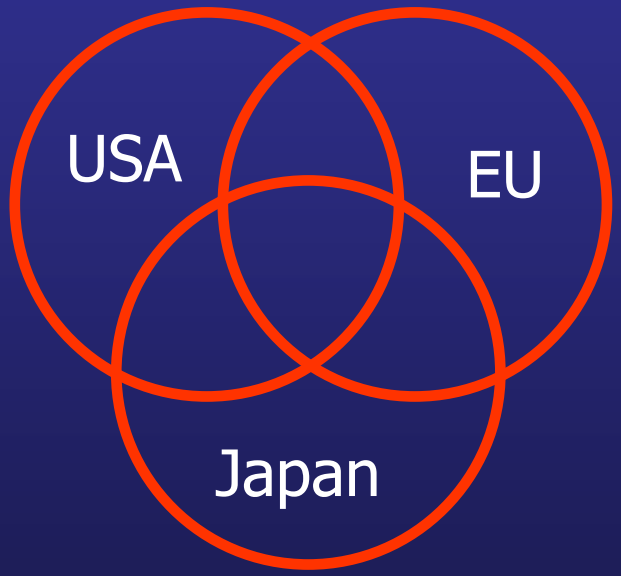
Mineo Yasuda†

34 Total Individuals

†IFTS, ‡Teratology Society, *MARTA, #MTA, wg = Working group

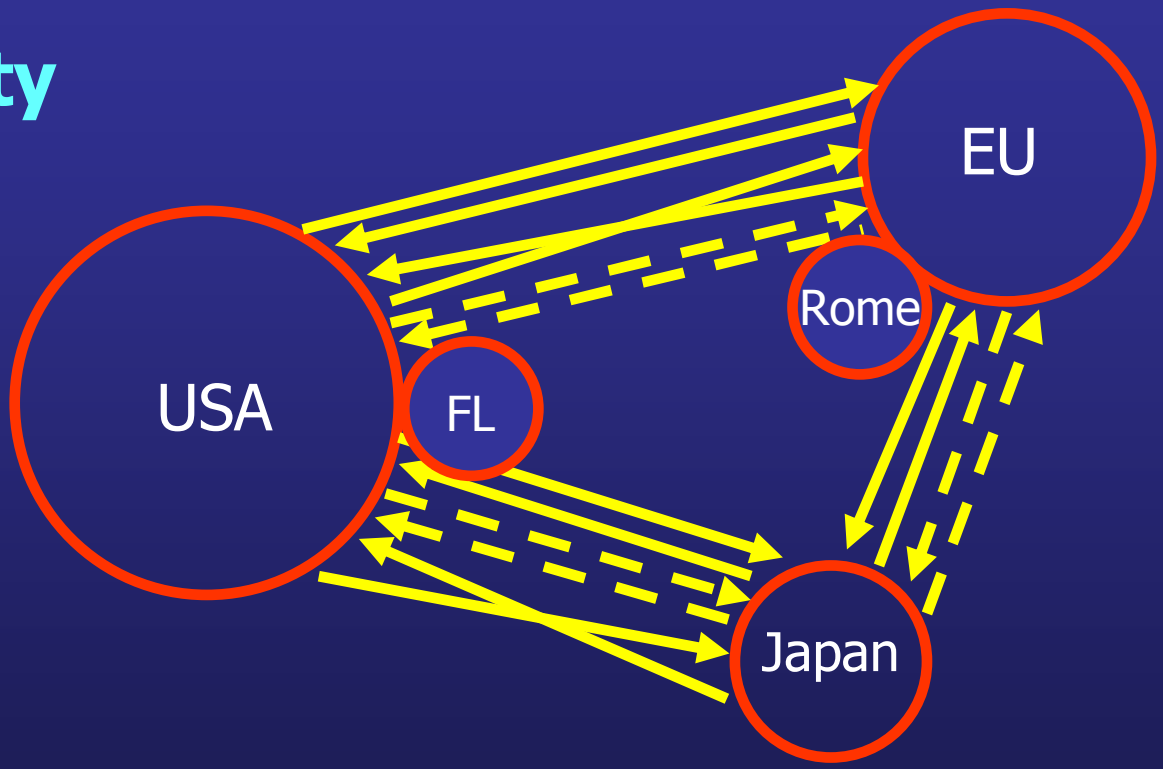
Version 1 - how it worked

The Ideal



Version 1 - how it worked

Reality



Version 1

External terms: 124

Visceral terms: 277

Skeletal terms: 467

} 868

Appendix A: Descriptive terms

Appendix B: Syndromes/combining terms

Berlin Workshops

1st (1995)

2nd (1998) – Defined Malformation vs. Variation

3rd (2000) – Classifying skeletal abnormalities
"Index of Agreement"

4th (2002) – Classifying external and visceral abnorms

5th (2005)
6th (2007) } Reasons for "gray zone anomalies"

7th (here we are)

Dr. Chahoud to provide the thunder

Version 2 (2002 - 2009)

EU:

Ruth Clark
Stephane Barbellion
Jochen Buschmann
Konstanze Grote
Keith Hazelden
Meg Parkinson

Japan:

Kohei Shiota
Makoto Ema
Michio Fujiwara
Masao Horimoto
Yojiro Ooshima

USA:

Susan Makris
Howie Solomon
Kok Wah Hew
Dave Wise

Version 2

Guiding Principles and Philosophies

- Document should serve the needs of:
  - Lab personnel
  - Regulatory scientists/reviewer
  - Scientists from other disciplines
- Terms should be descriptive and non-diagnostic
- Synonyms and related terms defined in Appendix and not repeated
- Ext, Visc, Skel tables should be expanded extensively to include findings that have been observed or that are reasonably likely
- Flexibility should be incorporated to accommodate procedures of various labs

Version 1

Alisphenoid
- Absent
- Fused
- Hole(s)
- Misshapen
- Small
- Incomplete ossification
- Unossified

Auditory ossicles
- Absent
- Fused
- Misshapen
- Unossified

11 total

Version 2

Alisphenoid

	LDW opinion
Absent	
Fused	
Hole	
Large (New)	?
Malpositioned (New)	Yes
Misshapen	
Small	
Supernumerary site (New)	?
Incomplete ossification	
Increased ossification (New)	?
Unossified	
Unossified area (New)	Yes

Auditory ossicles

Absent	
Fused	
Large (New)	?
Malpositioned (New)	?
Misshapen	
Small (New)	Yes
Supernumerary (New)	?
Supernumerary site (New)	?
Incomplete ossification (New)	?
Increased ossification (New)	?
Unossified	

23 total

Version 2

External terms: 166

Visceral terms: 534

Skeletal terms: 1020

} 1720 (↑~2-fold)

Maternal-Fetal abnormalities (n = 19)

Appendix A: Descriptive terms

Appendix B: Syndromes/combining terms

Appendix C: Alternative terms

Appendix D: Structural differences

Appendix E: Skeletal foramina & processes

The increase in the number of terms makes it important, if not mandatory, to group (i.e., merge) findings.

Is it possible to harmonize a method to group findings?

The Berlin Workshops have established the preferred classification for each term: Malformation or Variation

Consistent groupings within each classification are needed

Example groupings:

Fetuses with any:

- Heart malformations
- Gallbladder variations
- Skull bone malformations
- Thoracic vertebra malformations
- Supernumerary thoracic rib

Getting from Details to Conclusions

Data Collection

Group 1, Dam 1

F1	E1,2	V1.	S1,2,3
F2	E1		S4,5
F3	Normal		
F4	E3,4	v1,2	S3,5,6
F5	Normal		
etc			

Group 2 etc

Group 3 etc

Groiup 4 etc

Group 4, Dam 80

F1 …			
F10	E1,3,4	V3,4	S1,4,6,7
F11	E2,4	V5,6	S1,5,6,7
F12	E1,4	V3,4	S2,4,6
F13	Normal	V5	S3,6,9
F14	E4,8	V3,6	S4,8,10
F15	E1,2,4	V2,4	S1,2,4,6

1000 Fetuses, 2-10K entries

Data Reporting

Group:	1	2	3	4
	(Litter mean %)			
Domed head	.1	.2	.1	2.2
Cleft palate	0	.1	.2	.8
etc				
VSD	.1	0	.1	.6
Th vert M	0	.1	.2	.5
Bent rib	0	0	.1	.1
Ectrodactyly	0	0	.2	.2
Supern rib	10	12	9	22
etc				

Fetuses w/ (E, V, S, or any) Malformation

0.5	0.4	0.5	2.3

Fetuses w/ (E, V, S, or any) Variation

11	12	15	25

< 100 entries

Interpretation

Maternal

NO(A)EL = xx mg/kg/day
based on 11% ↓BWgain
(exposure margin = 10X)

Developmental

NO(A)EL = xx mkd
LO(A)EL = xxx mg/kg/day
based on cleft palate and supernumerary ribs

< 10 entries

Different forms of grouping

Harmonized "groupings" may assist other fields (e.g., product labels, *in vitro* alternatives)

Example: *in vitro* alternatives

Daston et al., A Different Approach to Validating Screening Assays for Developmental Toxicity (BDRB 89: 526-530, 2010)

- Developmental toxicant = an exposure to the developing organism that leads to a permanent adverse effect.
- Developmental nontoxicant = an exposure that does not cause permanent adverse effects.
- "This feature (*i.e., internal concentration*) captures an all-important aspect of real-world toxicology: the dose-response relationship."

What about severity/incidence and species differences at each exposure?

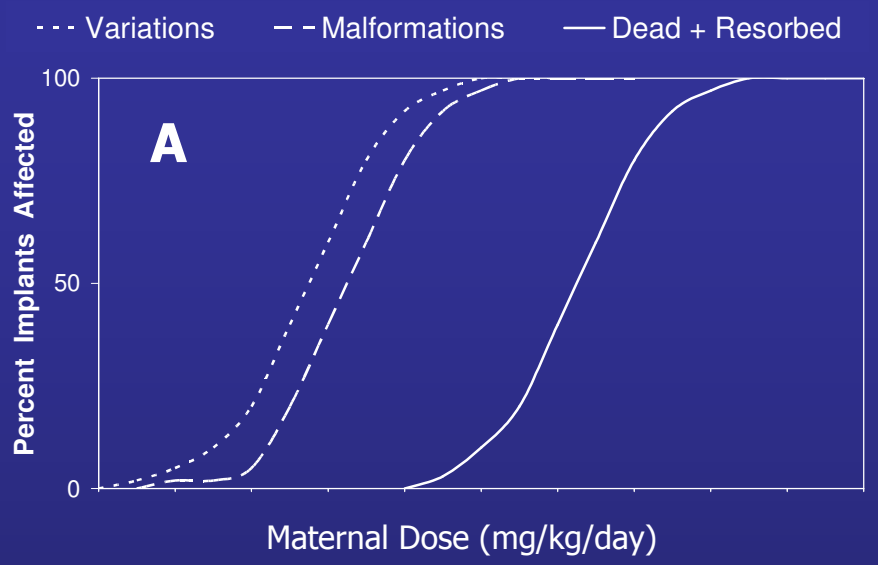
Hypothetical Outcomes

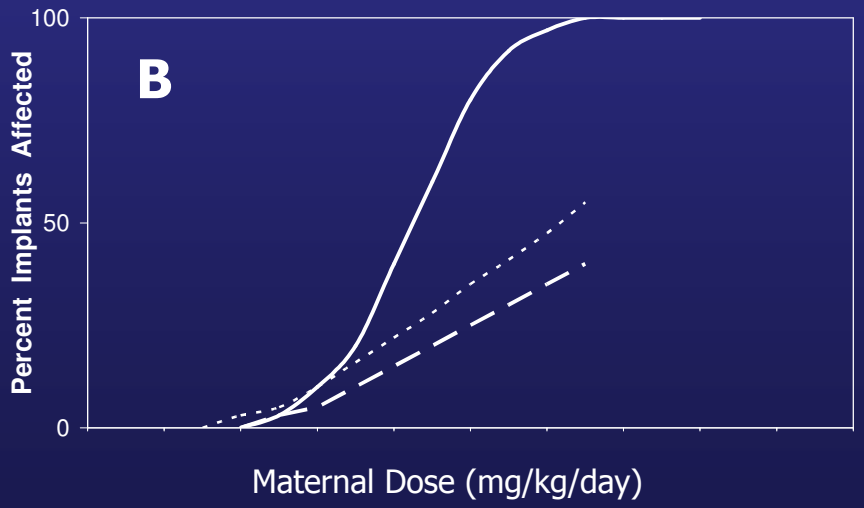
A = Malf & Var without lethality

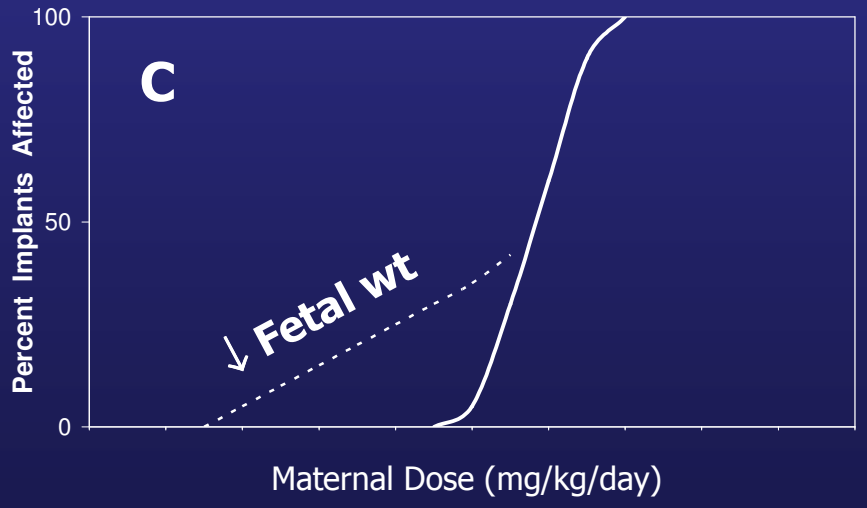
B = Combinations of Malf, Var, and lethality

C = ↓ growth → lethality with no Malf or Var

Adapted from Neubert et al. Curr Top Pathol 69: 242-324, 1980.







(Not) A New Idea?
(see Wang and Schwetz, TCM 7: 133-139, 1987)

"Developmental Tox Score"
=
Sum of developmental findings (to implants)
minus
Sum of maternal toxicity findings

Developmental Findings* = A + B + C + D

A = Mean (%) postimplantation loss

B = Mean (%) fetuses with ≥ 1 major malformation

C = Mean (%) fetuses with ≥ 1 minor malformation or variation

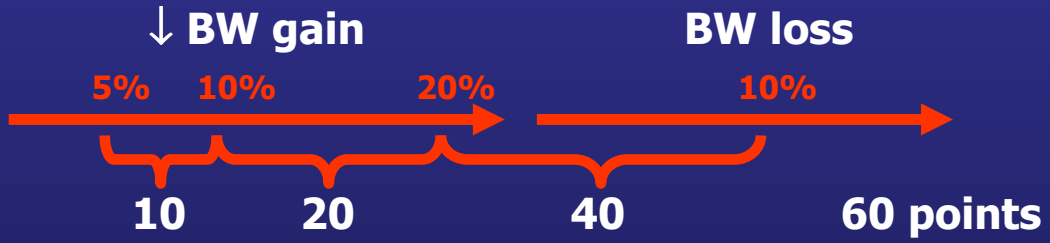
D = (% below control for) mean fetal body weight

* Deemed to be test article-related (± P≤0.05) and minus Control value.

Maternal Toxicity Findings* = E + F + G

E = % females found dead or euthanized early

F = Effects on maternal body weight



G = Subjective value for all other maternal toxicities (e.g., physical signs, food intake, gross changes)

* Deemed to be test article-related (± P≤0.05)

"Developmental Tox Score" Examples

#1

Wise et al., BDRB 80:57-68 (2007)
Vorinostat, Rat EFD: 5, 15, 50mkd.
50mkd: PI loss = 4.4-3.5=0.9; %V = Skeletal V = 49-14=35; D = female fetal wt = 24% below Control

	A PI loss	B %M	C %V	D fetal wt	E FD/ES	F BWG/BWL	G Other	(A+B+C+D)-(E+F+G)	Cmax (ng/mL)
50 mkd	0.9	0	35	24	0	0	5*	**55**	320
15 mkd	0	0	0	0	0	0	0	**0**	164
5 mkd	0	0	0	0	0	0	0	**0**	NA

* Based on decreases in some hematology parameters, AST, ALT, and Trigs in RF study at this dose level.

#2

Wise et al., BDRB 80:57-68 (2007)
Vorinostat, Rabbit EFD: 20, 50, 150mkd.
150mkd: %V = Skeletal V = 38-14=24, D = male fetal wt = 11% below Control

	A PI loss	B %M	C %V	D fetal wt	E FD/ES	F BWG/BWL	G Other	(A+B+C+D)-(E+F+G)	Cmax (ng/mL)
150 mkd	0	0	24	11	0	0	10*	**25**	326
50 mkd	0	0	0	0	0	0	0	**0**	114
20 mkd	0	0	0	0	0	0	0	**0**	NA

* Based on decreases in some hematology parameters and ALP in RF study at this and higher dose levels.

Future Efforts to Harmonize Terminology of Abnormalities in Developmental Toxicology

- *We need pictures*
- *Assign M, V, or IO to each term*
- *We need agreed upon groupings*