

Suitability of Version 2 terminology in non-human primates

8th Workshop on the Terminology in Developmental
Toxicology

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The Covance logo consists of the word "COVANCE" in a bold, blue, sans-serif font. A red curved line arches over the letters "V" and "A".

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Overview

- **Conclusion from workshop 2011**
- **Review of reference data and findings in dose groups**
- **Examples where we had a problem to include a finding to the list from 2011**
- **How to be included into the Terminology list**
- **Examples**
- **Conclusion**

Conclusion from workshop 2011:

After review of new document prior to workshop in 2011:

- In general, terminology for fetal examination can be used for primates
- Several special findings or structures need to be added

Subsequent review of reference data and findings in dose groups (86 Studies):

- Frequent and rare findings in NHP not found in the new terminology list
- Some structures have to be added too
- Appendix to Version 2 is in preparation (unfortunately not yet ready)
- No EFD studies since implementation of ICH S6 guidelines
- ➔ No experience with use of the list in a real study

Maternal-fetal findings

Umbilical cord –

- only two vessels (normal case is three vessels)
- edematous
- swollen
- red discolored
- twisted
- one artery, one vein
- not visible, dry (after delivery prior to c`section scheduled for GD 150)

Placenta -

- focus (could be reported as discolored)
- 2nd part discolored, swollen
- Necrosis
- Anemic

How to be included

Table 4

Maternal-Fetal Abnormalities

Region/Organ/ Structure	Observation	Definition/Note
Umbilical cord	Edematous	
	Only two vessels	
	One vein, one artery	
Placenta	Two veins, one artery	
	Twisted	
	Dry	After abortion or delivery
	Evaluation not possible	After abortion or delivery
Placenta	Not visible	After abortion or delivery
	Yellow focus	Describe which part
	Necrosis	Describe which part
	Yellow deposits	Describe which part
Placenta	Anemic	

External findings

- **Prepuce not or incompletely patent**
- Genital region – enlarged
- Craniofacial region - amniotic banding
- Anterior vulva region – reddened
- Ear/s - additional tissue flag on lobule of auricle
- Sternum - bent outwards/inwards
- Thorax – misshapen
- External genitals – absent, reduced in size, swollen, red discoloured
- **Head – poor hair**
- **Fur findings in general for fetuses collected GD 150**
- Tail constrictions, incisures, flattened
- **Foot joint misshapen**
- **Abnormal position of fingers/toes**
- **Finger/toe nail - reduced in size, absent**

External, skeletal

Monkeys have hands, feet, fingers, toes and nails, not paws and claws



Fetal „forepaw“ and use of hands by adult monkey

External findings

- Additional nipples (three or four)
- Rare variation, also observed in adults



How to be included

Table 1
External Abnormalities

Region/Organ/ Structure	Observation	Definition/Note
General		
Fur	Thin/poor Absent	Specify region Specify region
Head		
Craniofacial region	Amniotic banding Asymmetric Brown-focus between eyes	
Eyes		
Discharge	Clear Discolored	

How to be included

Table 1

External Abnormalities (cont.)

Region/Organ/ Structure	Observation	Definition/Note
Ears	Tissue flag	
Jaw	Deposits	
Trunk		
Genital region	Vulva discolored Large Spots	
Prepuce	Not patent Displaced	
Penis	Short Malpositioned Misshapen Long	

How to be included

Table 1

External Abnormalities (cont.)

Region/Organ/ Structure	Observation	Definition/Note
Thorax	Nipple	Supernummary Absent
	Tail	Single Flattened Kinked Tissue ball
Forelimb/Hindlimbs	Joints	More than two nipples Describe region Describe region Tail end Stiff Hyperflexion Hyperextension

How to be included

Table 1

External Abnormalities (cont.)

Region/Organ/ Structure	Observation	Definition/ Note
Forelimb/Hindlimbs		
Hand/Foot	Absent Fused Malrotated Hyperflexion Hyperextension	
Finger/Toes	Absent Few Fused Large Malpositioned Misshapen Pendulous Small Supernumerary Discolored Thick Additional nail Nail bent Nail absent	

Visceral findings

- Adrenals – soft consistency
- Amnion fused to cerebral hemispheres and cerebellum
- Cerebellum hypoplastic
- Eyes – discharge of liquid
- Heart – hematoma at apex
- Spleen – firm consistency
- Testes – blood shot

Visceral findings

Stomach

- ❖ foci at cardia
- ❖ foci at cardia region
- ❖ foci at fundus
- ❖ hemorrhage at mucosa
- ❖ hemorrhage at cardia
- ❖ hemorrhage at cardia region
- ❖ reddened cardia
- ❖ hemorrhage
- ❖ hemorrhage at fundus
- ❖ hemorrhage at pylorus

Visceral findings

Further examples:

Thymus:

- ❖ Multiple small hemorrhages
- ❖ Small red spots
- ❖ Red focus
- ❖ Reddened
- ❖ Red spotted
- ❖ Bright red patterned
- ❖ Red patterned
- ❖ Black-red discolored

Visceral findings

Structures not included in the new terminology:

- ❖ Salivary glands
- ❖ Lymphnodes

How to be included

Table 2
Visceral Abnormalities

Region/Organ/ Structure	Observation	Definition/Note
Brain	Amnion Cerebellum Hemispheres	fused to hemisphere fused to cerebellum asymmetric asymmetric
Salivary gland		discolored
Heart	Pericardium	Fatty
Esophagus		Mucosa discolored

How to be included

Table 2

Visceral Abnormalities (cont.)

Region/Organ/ Structure	Observation	Definition/Note
Stomach		
All areas	red foci	
Cardia	discolored	
	red focus/l	
	punctiform hemorrhages	
fundus	discolored	
	red focus/l	
	punctiform hemorrhages	
Mucosa	discolored	
Content	discolored	
Pylorus	discolored	

How to be included

Table 2

Visceral Abnormalities (cont.)

Region/Organ/ Structure	Observation	Definition/Note
Lymphnodes		
Mandibular	red foci	
Mesenteric	red foci	
Axillary	red foci	

Skeletal findings

Skull, base, GD 100, to be examined:

Ala minor ossis sphenoidale

Ala major ossis sphenoidale

Os frontale

Os parietale

Os occipitale

Pars lateralis ossis occipitale

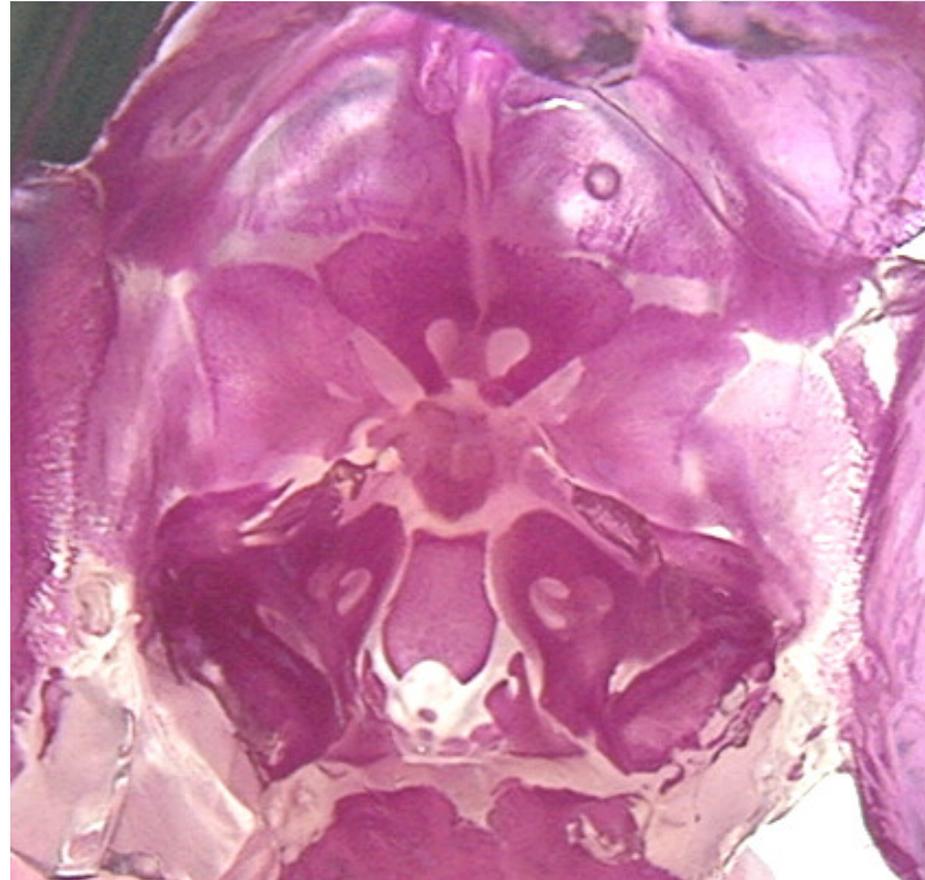
Foramen magnum

Clivus

Os petrosum

Sella turcica

Os temporale



Skeletal findings

At GD 150 ossification of tarsal and carpal bones:

Hand:

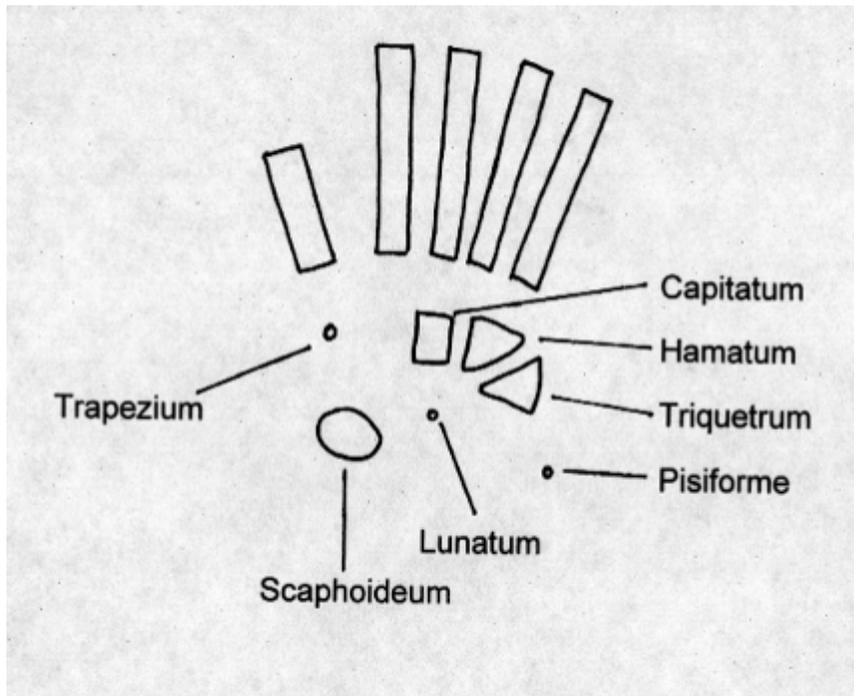
- Trapezium
- Triquetrum
- Scaphoideum
- Capitatum
- Hamatum
- Lunatum
- Pisiforme
- Marmosets: central bone

Foot:

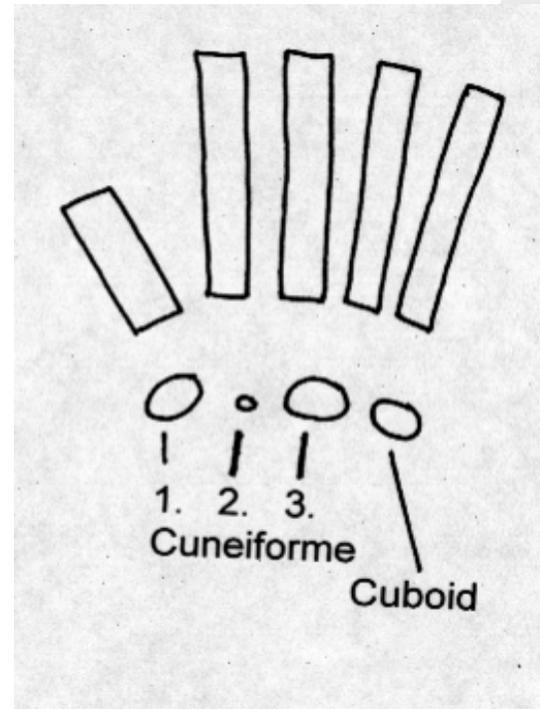
- Cuneiforme 1 to 3
- Cuboideum

Skeletal findings

Hand, normal ossification GD 150



Foot, normal ossification GD 150



Skeletal findings

Penial bone



How to be included

Table 3

Skeletal Abnormalities

Region/Organ/ Structure	Observation	Definition/Note
Skull		
Cranial base	Flat	
Clivus	Absent Fused Hole Large Malpositioned Misshapen Small Split Bipartite ossification Incomplete ossification Increased ossification Isolated ossification site Unilateral ossification Unossified Unossified area Unossified line	

How to be included

Table 3

Skeletal Abnormalities (cont.)

Region/Organ/ Structure	Observation	Definition/Note
Sella turcica	Absent Fused Hole Large Malpositioned Misshapen Small Split Bipartite ossification Incomplete ossification Increased ossification Isolated ossification site Unilateral ossification Unossified Unossified area Unossified line	

How to be included

Table 3

Skeletal Abnormalities (cont.)

Region/Organ/ Structure	Observation	Definition/Note
Pelvic girdle		
Penial bone	Absent Large Malpositioned Misshapen Small Incomplete ossification Increased ossification Isolated ossification site Displaced	

How to be included

Table 3

Skeletal Abnormalities (cont.)

Region/Organ/ Structure	Observation	Definition/Note
Forelimb		
Radius	Fused to ulna	
Capitulum	Incomplete ossification	
	Unossified	
Centrale	Unossified	
Hamatum	Incomplete ossification	
	Unossified	
Lunatum	Incomplete ossification	
	Unossified	
Metacarpal	Large	

How to be included

Table 3
Skeletal Abnormalities (cont.)

Region/Organ/ Structure	Observation	Definition/Note
Forelimb	Pisiforme	Incomplete ossification Unossified
	Scaphoideum	Incomplete ossification Unossified
	Trapezium	Incomplete ossification Unossified
	Trapezoideum	Unossified
	Triquetrum	Incomplete ossification Unossified

How to be included

Table 3

Skeletal Abnormalities (cont.)

Region/Organ/ Structure	Observation	Definition/Note
Hindlimb		
Tibia	Fused to fibula	
Talus	Incomplete ossification	
Cuboideum	Incomplete ossification Unossified	
Cuneiforme	Incomplete ossification Unossified	
Naviculare	Unossified	

Example for use of terminology Control fetus

Old reporting	New terminology
<p>Prepuce</p> <p>V - not patent</p>	<p>Trunk</p> <p>Prepuce not patent</p>
<p>Stomach</p> <p>V - light red focus/i, cardia</p>	<p>Stomach</p> <p>Cardia discolored, red focus/i</p>
<p>Inspection of fixed heart</p> <p>no abnormalities detected</p>	<p>Heart</p> <p>no abnormalities detected</p>
<p>Skull</p> <p>V - frontal, right, incompletely ossified (approx. 0.5 mm in diameter)</p> <p>V - occipital, incompletely ossified</p> <p>V - petrosal, bilateral, incompletely ossified</p> <p>V - sella turcica, incompletely ossified</p>	<p>Skull</p> <p>Frontal incomplete ossification</p> <p>Occipital incomplete ossification</p> <p>Petrosal incomplete ossification</p> <p>Sella turcica incomplete ossification</p>

Example for use of terminology Control fetus

Old reporting	New terminology
<p>Vertebral column</p> <p>V - additional ossification site prior to normal first</p>	<p>Vertebra</p> <p>Atlas Supernumerary site</p> <p>Or</p> <p>Vertebra, General Supernumerary site</p>
<p>Sternum</p> <p>V - sternebra(e), 1, 2, 6, 7, not ossified</p> <p>V - sternebra(e), 5 , incompletely ossified</p>	<p>Sternebra</p> <p>Sternebra unossified 1, 2, 6, 7</p> <p>Sternebra incomplete ossification,5</p>

Example for use of terminology

Thalidomide fetus – Selected findings

<p>Extremity/ies - external</p> <p>M - upper and lower, shortened, severe and malformed</p> <p>M - hands bilateral absent, only 1 finger present</p> <p>M - foot, left, 6 toes</p> <p>M - foot, right, 7 toes</p> <p>V - vertebra(e), 48 to 50, misaligned</p>	<table> <tr> <td>Forelimb</td> <td>Small</td> </tr> <tr> <td>Hindlimb</td> <td>Small</td> </tr> <tr> <td>Hand</td> <td>Absent</td> </tr> <tr> <td>Hand</td> <td>Oligodactyly</td> </tr> <tr> <td>Foot</td> <td>Polydactyly</td> </tr> <tr> <td colspan="2" style="text-align: center;">Absent hand with oligodactyly?</td> </tr> <tr> <td>Forelimb</td> <td>Oligodactyly?</td> </tr> </table>	Forelimb	Small	Hindlimb	Small	Hand	Absent	Hand	Oligodactyly	Foot	Polydactyly	Absent hand with oligodactyly?		Forelimb	Oligodactyly?
Forelimb	Small														
Hindlimb	Small														
Hand	Absent														
Hand	Oligodactyly														
Foot	Polydactyly														
Absent hand with oligodactyly?															
Forelimb	Oligodactyly?														
<p>Shoulder girdle - skeletal</p> <p>M - clavicle, bilateral, misshapen</p> <p>V - scapula, bilateral, incompletely ossified</p> <p>M - scapula, bilateral, misshapen</p>	<table> <tr> <td>Clavicle</td> <td>Misshapen</td> </tr> <tr> <td>Scapula</td> <td>Misshapen</td> </tr> <tr> <td>Scapula ossification</td> <td>incomplete</td> </tr> </table>	Clavicle	Misshapen	Scapula	Misshapen	Scapula ossification	incomplete								
Clavicle	Misshapen														
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Scapula ossification	incomplete														

Example for use of terminology

Thalidomide fetus – selected findings

<p>Forelimbs – skeletal</p> <p>M - humerus, left, severely shortened</p> <p>M - humerus, right, slightly shortened</p> <p>M - humerus, bilateral, malpositioned - lateral to scapula</p> <p>M - radius, bilateral, absent</p> <p>M - ulna, bilateral, absent</p> <p>V - phalanx, distal, left, incompletely ossified</p> <p>V - phalanx, proximal, right, thickened</p> <p>M - once, bilateral, phalanges distal, medial and proximal, present</p>	<table> <tr> <td>Humerus</td> <td>Short Malpositioned</td> </tr> <tr> <td>Radius</td> <td>Absent</td> </tr> <tr> <td>Ulna</td> <td>Absent</td> </tr> <tr> <td>Forelimb phalanx</td> <td>Incomplete ossification</td> </tr> <tr> <td>Forelimb phalanx</td> <td>Thickened</td> </tr> <tr> <td>Forelimb phalanx</td> <td>Present, one, distal, medial, proximal</td> </tr> </table>	Humerus	Short Malpositioned	Radius	Absent	Ulna	Absent	Forelimb phalanx	Incomplete ossification	Forelimb phalanx	Thickened	Forelimb phalanx	Present, one, distal, medial, proximal
Humerus	Short Malpositioned												
Radius	Absent												
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Forelimb phalanx	Present, one, distal, medial, proximal												

Example for use of terminology

Thalidomide fetus – selected findings

<p>Hindlimbs - skeletal</p> <p>M - femur, bilateral, vestigial</p> <p>M - fibula, bilateral, absent</p> <p>M - tibia, bilateral, severe malformed, triangular, vestigial</p> <p>M - foot, bilateral, 1. to 6. toe, metatarsal, phalanges distal, medial and proximal, present</p> <p>V - foot left, phalanx, medial, incompletely ossified</p> <p>M - foot, right, additional 7. toe, malpositioned</p> <p>M - foot, right, additional 7. toe, phalanges distal and medial, present</p> <p>M - calcaneus, bilateral, misshapen</p> <p>V- calcaneus, bilateral, incompletely ossified</p> <p>M - metatarsal, 2, 3, right, slightly shortened, malpositioned</p>	<table border="0"> <tr> <td>Femur</td> <td>Short?</td> </tr> <tr> <td>Fibula</td> <td>Absent</td> </tr> <tr> <td>Tibia</td> <td>misshapen</td> </tr> <tr> <td></td> <td>Short?</td> </tr> <tr> <td>Hindlimb phalanx</td> <td>Present, 1 to 6 toe, distal, medial, proximal</td> </tr> <tr> <td></td> <td>Present, 7, distal, medial</td> </tr> <tr> <td>Metatarsal</td> <td>Present; 1 to 6</td> </tr> <tr> <td></td> <td>Supernumerary</td> </tr> <tr> <td></td> <td>Malpositioned</td> </tr> <tr> <td>Calcaneus</td> <td>Misshapen</td> </tr> <tr> <td>Metatarsal</td> <td>Malpositioned</td> </tr> <tr> <td></td> <td>Short</td> </tr> </table>	Femur	Short?	Fibula	Absent	Tibia	misshapen		Short?	Hindlimb phalanx	Present, 1 to 6 toe, distal, medial, proximal		Present, 7, distal, medial	Metatarsal	Present; 1 to 6		Supernumerary		Malpositioned	Calcaneus	Misshapen	Metatarsal	Malpositioned		Short
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15 mg/kg Thalidomide on days 26, 27, 28 p.c.



Conclusion

Use of new terminology for DART studies in NHP (cynomolgus, marmoset) is possible

The appendix for Version 2 is in preparation

Agreed terminology is essential for electronic data capture which is upcoming for NHP DART studies but not yet implemented

For ePPND studies, the agreed terminology should be used as far as possible for the teratology assessment at external examination and necropsy

Questions?

