# 25 YEARS *DEVTOX* WORKSHOPS: HISTORIC BACKGROUND, SCIENTIFIC AND TECHNICAL IMPROVEMENTS

Rupert Kellner

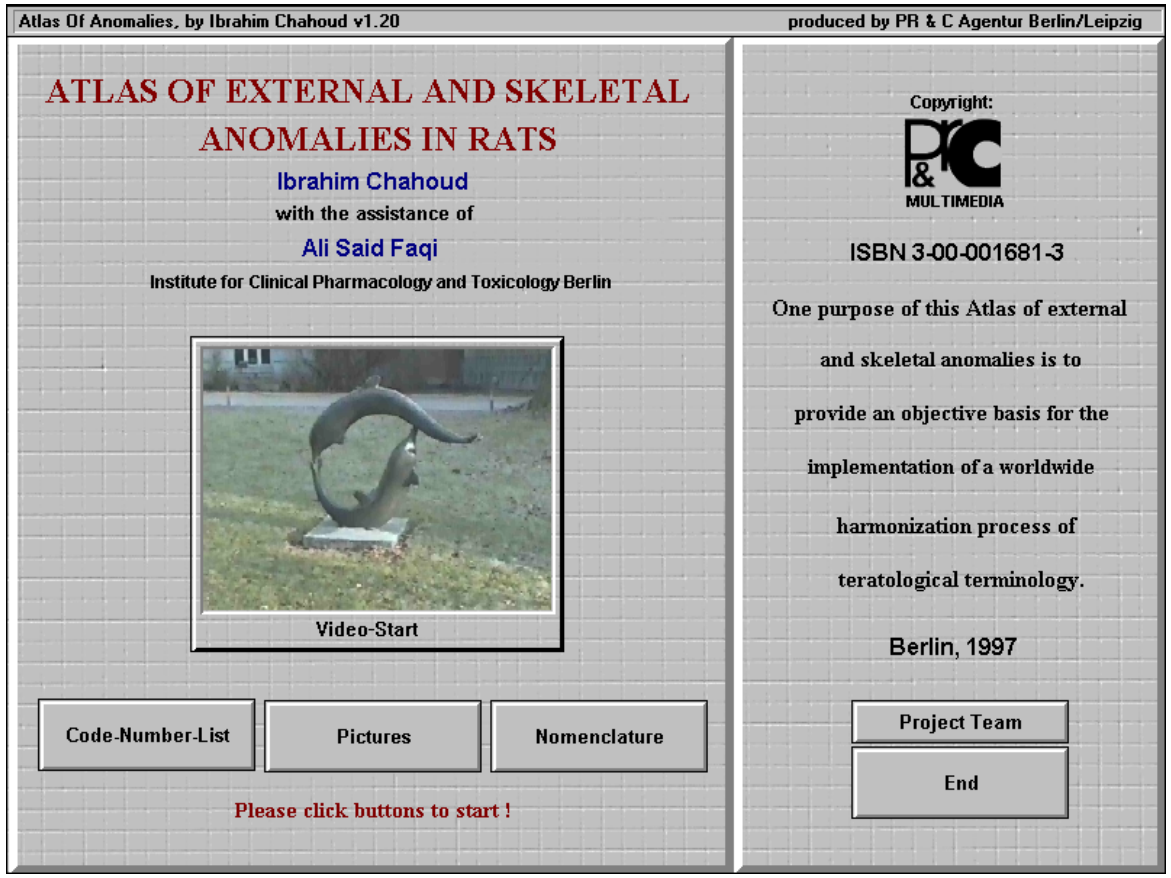
# OVERVIEW

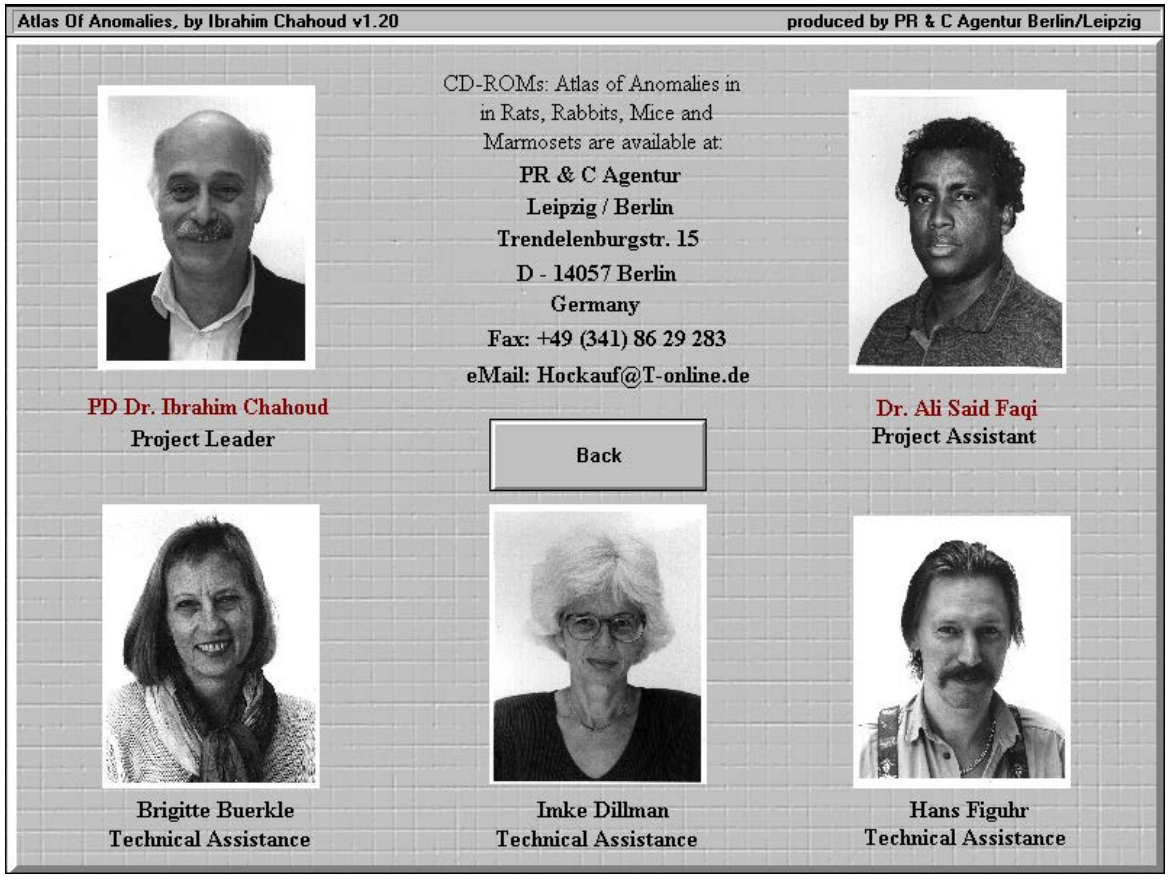
- Starting point of *Dev*Tox
- First presentation on the Web
- Technical improvements
- Translation of *Dev*Tox
- *Dev*Tox perspectives

# Atlas of Anomalies in Rats

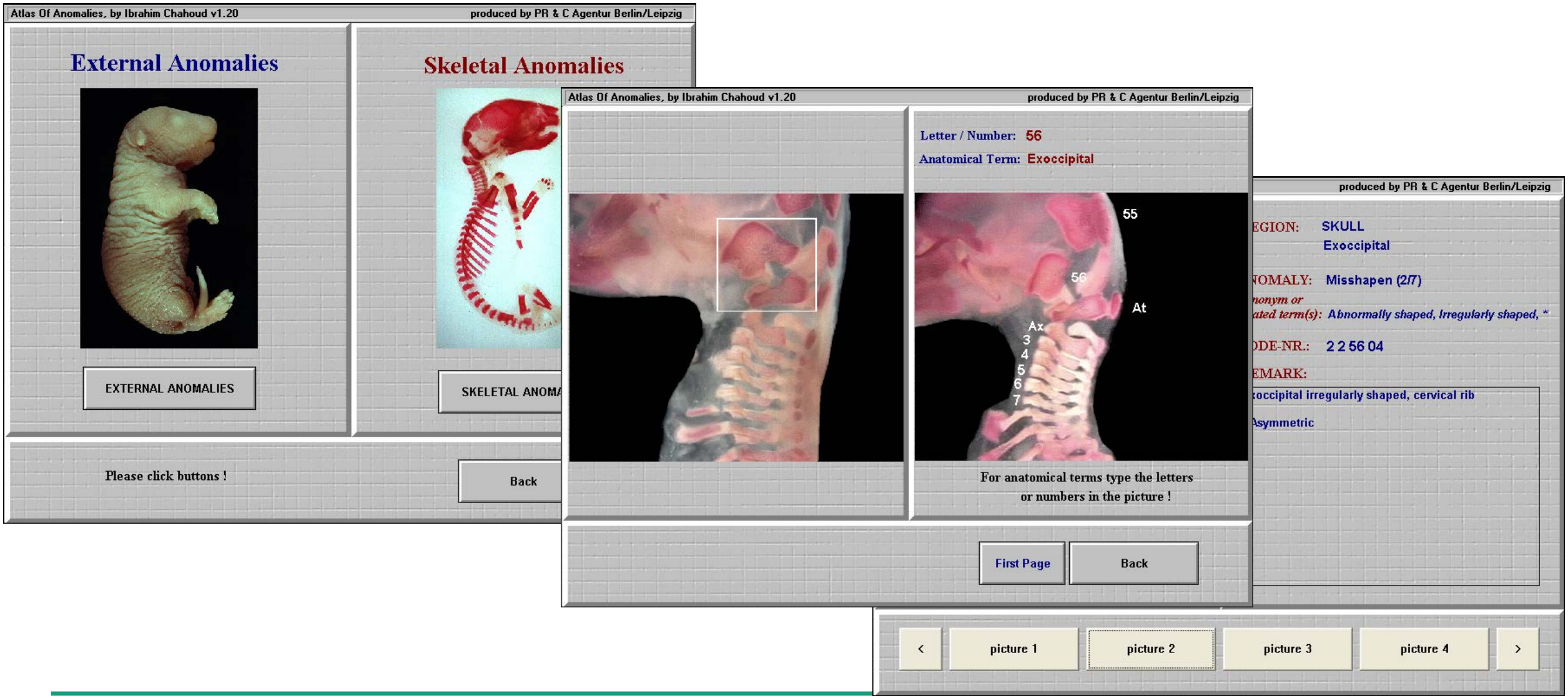

- CD-ROM: April 1997
- Based on IFTS harmonized glossary
- 140 findings
- 350 images

# Atlas of Anomalies in Rats



# Atlas of Anomalies in Rats



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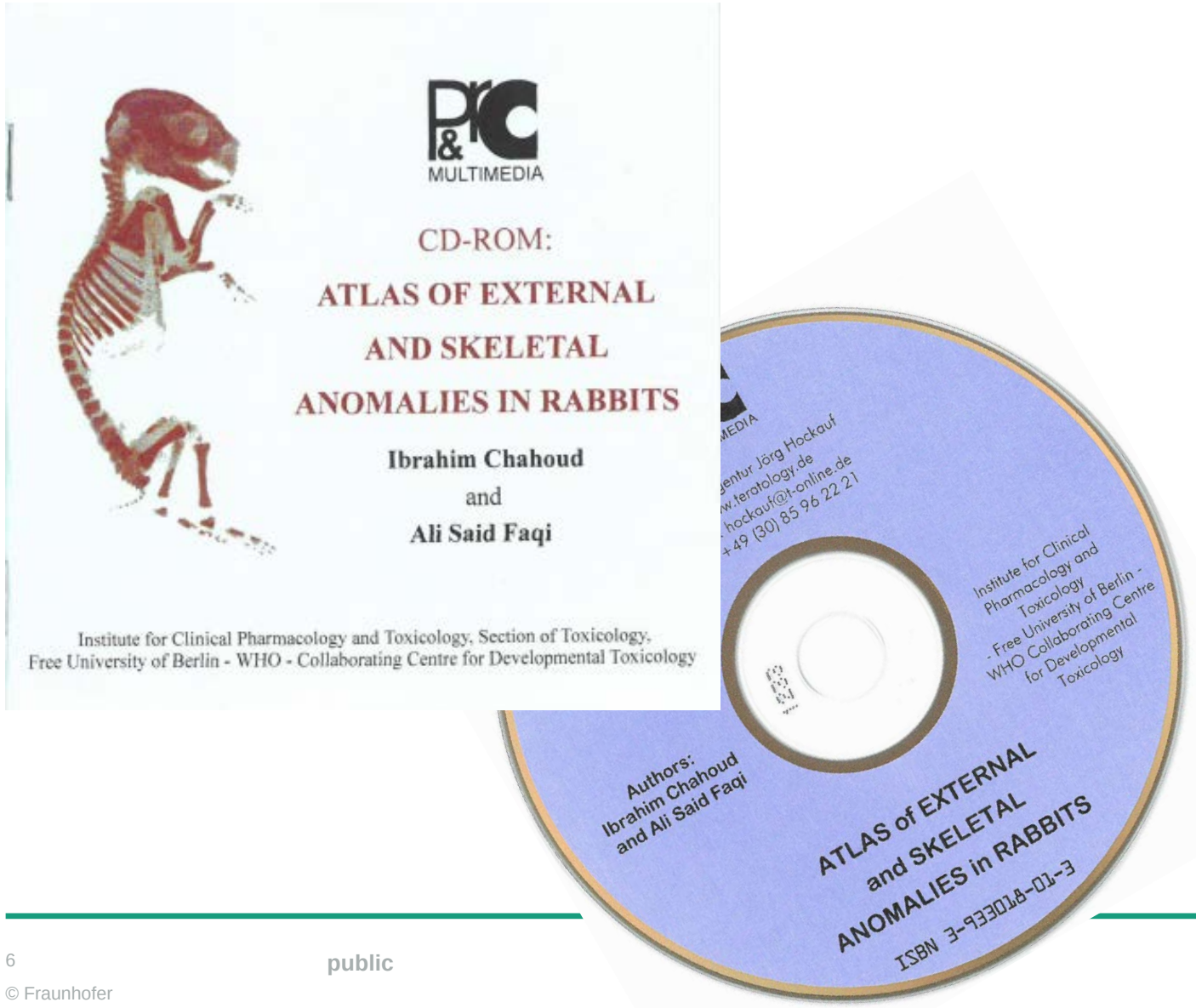
# Atlas of Anomalies in Rabbits




- CD-ROM: August 1997
- Based on IFTS harmonized glossary
- 104 findings
- 205 images

# Atlas of Anomalies in Rabbits


- Additional CD-ROMs
- Marmosets
  October 1998
- Mice
  April 1999

# *Dev*Tox: Developmental toxicology

- Initiated in 1999
- Project funded by the Federal Institute for Risk Assessment (BfR, Berlin)
- Collaboration with:
  - Institute of Clinical Pharmacology and Toxicology, Department of Toxicology (Charité, Berlin)
  - Fraunhofer Institute for Toxicology and Experimental Medicine (ITEM, Hannover)

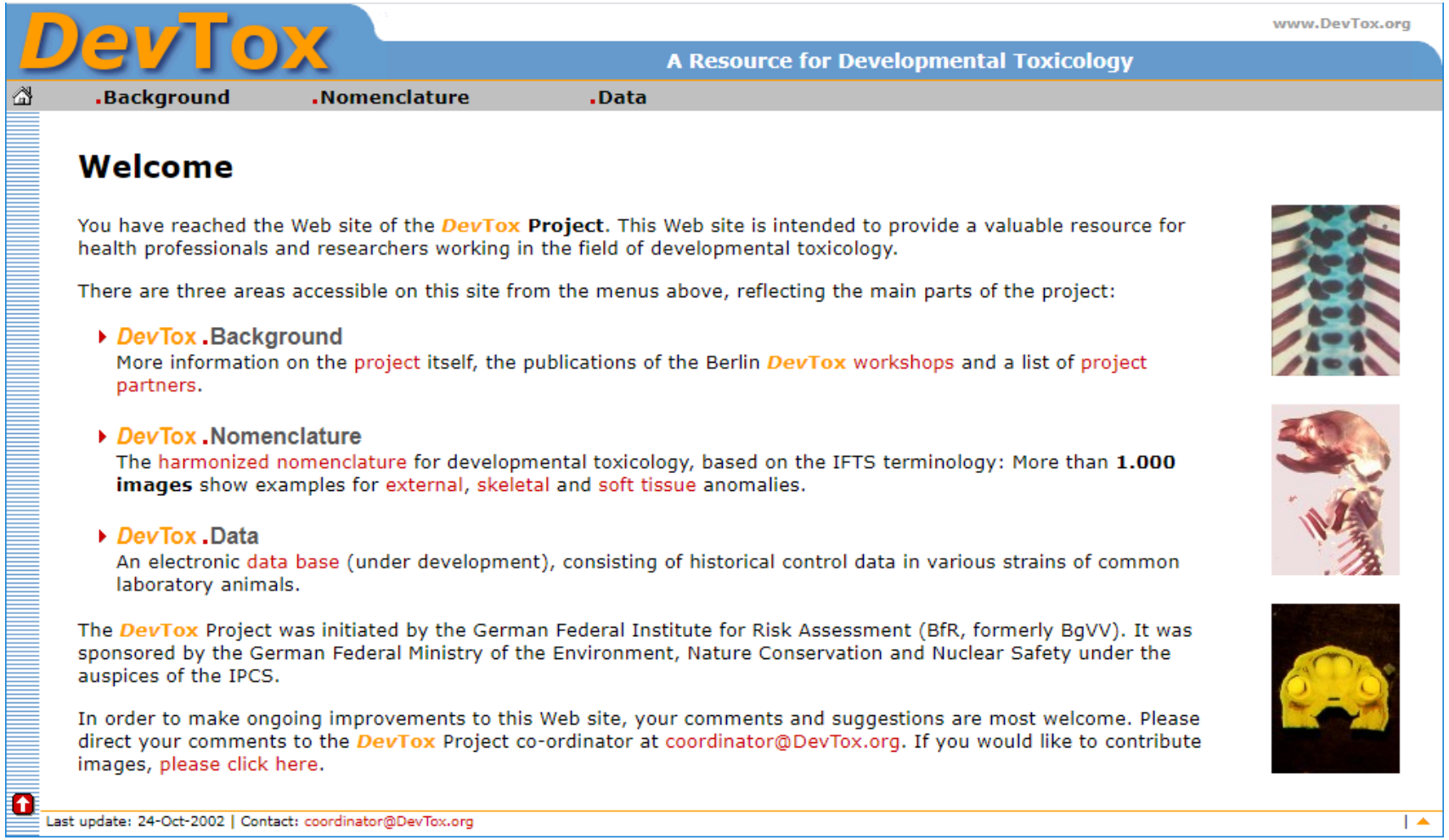
BfR
Risiken erkennen – Gesundheit schützen

CHARITÉ
UNIVERSITÄTSMEDIZIN BERLIN

Fraunhofer
ITEM

- Harmonized nomenclature for developmental toxicology
- Public Website: https://www.devtox.org

# *Dev*Tox Version 1




- Website
  - HTML pages
- Version from 2002
- >1000 images

# *Dev*Tox Version 1 (2002)


# *Dev*Tox Version 1 (2002)

Home | Help | Configuration — DevTox — Rat | Mouse | Rabbit | Other

External Findings | Skeletal Findings | Soft Tissue Findings

show as ○ List View ● Tree View

| Skeletal Findings | ① | ② | ③ | ④ |
|---|---|---|---|---|
| Skull | ✓ | ✓ | ✓ | ✓ |
| Alisphenoid | ✓ | ✓ | ✓ | ✓ |
| Auditory ossicles | ✓ | ✓ | ✓ | ✓ |
| Basioccipital | ✓ | ✓ | ✓ | ✓ |
| Basisphenoid | ✓ | ✓ | ✓ | ✓ |
| Exoccipital | ✓ | ✓ | ✓ | ✓ |
| Frontal | ✓ | ✓ | ✓ | ✓ |
| Hyoid | ✓ | ✓ | ✓ | ✓ |
| Interparietal | ✓ | ✓ | ✓ | ✓ |
| Lacrimal | ✓ | ✓ | ✓ | ✓ |
| Mandible | ✓ | ✓ | ✓ | ✓ |
| Maxilla | ✓ | ✓ | ✓ | ✓ |
| Nasal | ✓ | ✓ | ✓ | ✓ |
| Palatine | ✓ | ✓ | ✓ | ✓ |
| Parietal | ✓ | ✓ | ✓ | ✓ |
| Premaxilla | ✓ | ✓ | ✓ | ✓ |
| Presphenoid | ✓ | ✓ | ✓ | ✓ |
| Squamosal | ✓ | ✓ | ✓ | ✓ |
| Supraoccipital | ✓ | ✓ | ✓ | ✓ |
| Tympanic annulus | ✓ | ✓ | ✓ | ✓ |
| Vomer | ✓ | ✓ | ✓ | ✓ |
| Zygomatic | ✓ | ✓ | ✓ | ✓ |
| Vertebra | ✓ | ✓ | ✓ | ✓ |
| Cervical vertebra | ✓ | ✓ | ✓ | ✓ |
| Cervical centrum | ✓ | ✓ | ✓ | ✓ |
| Cervical centrum cartilage | ✓ | ✓ | ✓ | ✓ |
| Cervical arch | ✓ | ✓ | ✓ | ✓ |
| Thoracic vertebra | ✓ | ✓ | ✓ | ✓ |
| Thoracic centrum | ✓ | ✓ | ✓ | ✓ |

| Exoccipital | ① | ② | ③ | ④ |
|---|---|---|---|---|
| Absent | M | M | M | M |
| Fused | M | M | M | M |
| Hole(s) | ✓ | ✓ | ✓ | ✓ |
| Incomplete ossification | V | V | V | V |
| Misshapen | ✓ | ✓ | ✓ | ✓ |
| Sma | | | | |
| Uno | | | | |

Home | Locations | Findings | ← → | Manuscript | Comments | Help — DevTox — Rat | Mouse | Rabbit | Other

**Exoccipital – Misshapen** — **Skeletal finding**

**Synonym(s):** Abnormally shaped; Irregularly shaped
**Non-preferred term(s):** –

**Definition:**
Abnormally shaped [Not to be used to describe sites of incomplete ossification].

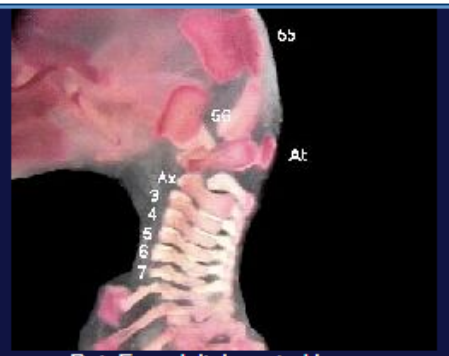
**Notes:**
–

Fig. 1: Exoccipital bone fused with a bone of atlas-like structure
*Additional finding:* Cervical rib

Fig. 2: Exoccipital bone irregularly shaped
*Additional finding:* Cervical rib

Fig. 3: –

Control




Rat, Exoccipital: control image

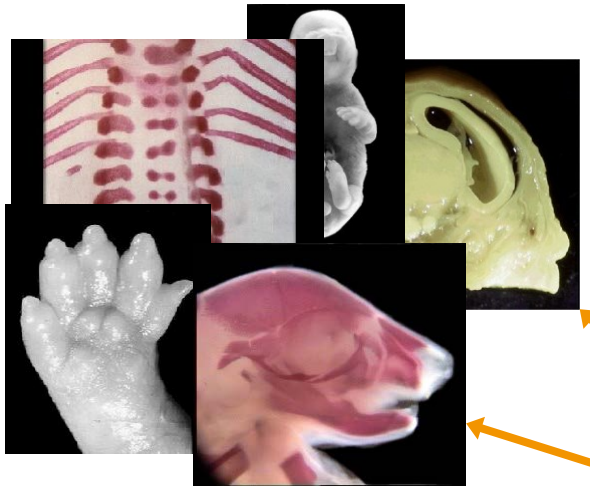
**Fig. 2:** Rat, Exoccipital – Misshapen.
Exoccipital bone irregularly shaped
*Additional finding:* Cervical rib

# *Dev*Tox Version 1 (2002)

- External Findings
  - 396 images (288 anomalies, 108 control)
- Skeletal Findings
  - 570 images (390 anomalies, 180 control)
- Soft Tissue Findings
  - 92 images (79 anomalies, 13 control)
- Species
  - Rat: 532 images
  - Mouse: 392 images
  - Rabbit: 134 images
  - Other (placeholder)

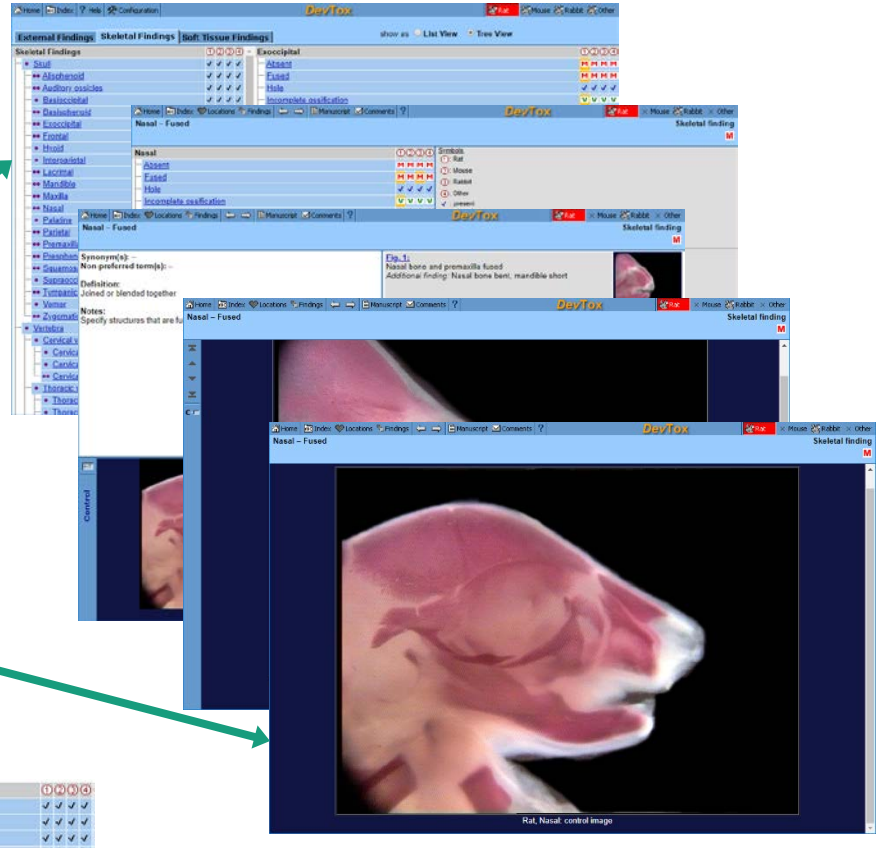
- HTML tree
  - 4340 files
  - 9549 files
  - 4290 files
- Difficult to handle
- Advantage:
  Offline usage (could be put on CD)

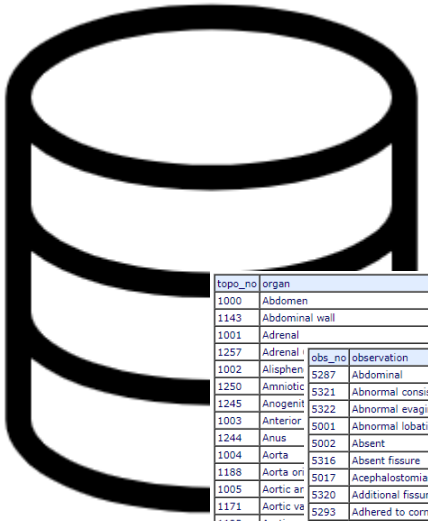
# *Dev*Tox Version 2 (2004)



32 files

php





| topo_no | organ | paired | species_def |
|---|---|---|---|
| 1000 | Abdomen | - | 111111111 |
| 1143 | Abdominal wall | - | 111111111 |
| 1001 | Adrenal | P | 111111111 |
| 1257 | Adrenal | | |
| 1002 | Alisphen | | |
| 1250 | Amniotic | | |
| 1245 | Anogenit | | |
| 1003 | Anterior | | |
| 1244 | Anus | | |
| 1004 | Aorta | | |
| 1188 | Aorta or | | |
| 1005 | Aortic ar | | |
| 1171 | Aortic va | | |
| 1193 | Aorticop | | |
| 1159 | Aqueous | | |
| 1189 | Artery | | |
| 1140 | Atlas, ve | | |
| 1172 | Atrial sej | | |
| 1173 | Atrium | | |
| 1006 | Auditory | | |
| 1174 | A-V cana | | |
| 1175 | A-V ostiu | | |
| 1176 | A-V sept | | |
| 1007 | Azygos v | | |
| 1008 | Basiocci | | |
| 1009 | Basisphe | | |

| obs_no | observation | species_def |
|---|---|---|
| 5287 | Abdominal | 111111111 |
| 5321 | Abnormal consistency | 111111111 |
| 5322 | Abnormal evagination | 111111111 |
| 5001 | Abnormal lobation | 111111111 |
| 5002 | Absent | 111111111 |
| 5316 | Absent fissure | 111111111 |
| 5017 | Acephalostomia | 111111111 |
| 5320 | Additional fissure | 111111111 |
| 5293 | Adhered to cornea | 111111111 |
| 5349 | Altered consistency | 111111111 |
| 5336 | Altered surface texture | 111111111 |
| 5294 | Altered texture | 111111111 |
| 5027 | Anencephaly | 111111111 |
| 5028 | Aneurysm | 111111111 |
| 5262 | Asymmetric | 111111111 |
| 5264 | Asymmetric ossification | 111111111 |
| 5040 | Atretic | 111111111 |
| 5043 | Bent | 111111111 |
| 5342 | Bifurcated | 111111111 |
| 5310 | Bilateral | 111111111 |
| 5044 | Bilobed | 111111111 |
| 5045 | Bipartite ossification | 111111111 |





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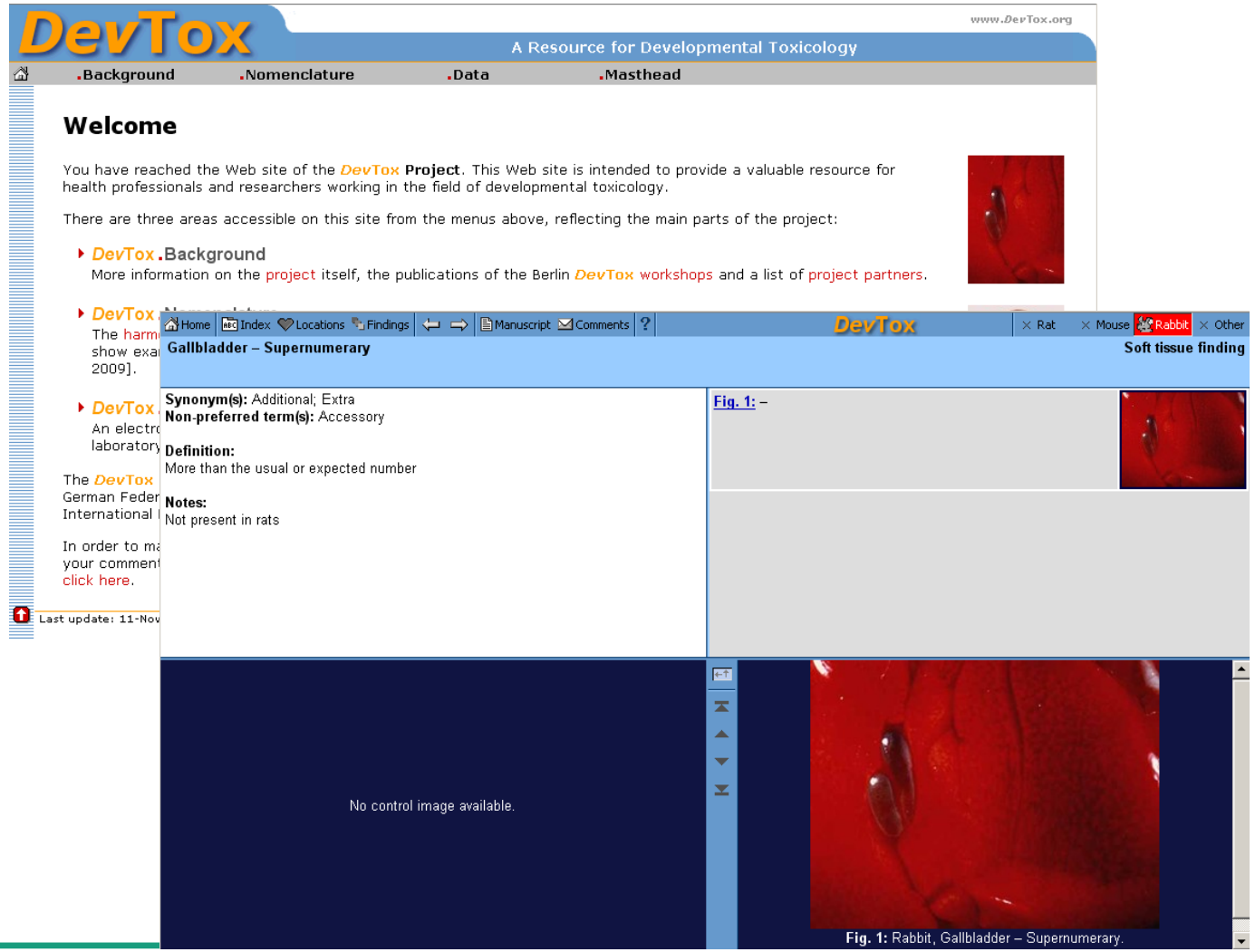
# DevTox Images in Version 2 (2009)

- Last release on December 09, 2009
  - with 371 new images
- >1.700 images
- Anomalies per species
  - Rat: 677 images
  - Mouse: 259 images
  - Rabbit: 314 images
  - Other: 53 images

    incl. Hamster, Monkey, Quail
- New findings



# New Terminology


Reproductive Toxicology 28 (2009) 371–434

Contents lists available at ScienceDirect

Reproductive Toxicology

journal homepage: www.elsevier.com/locate/reprotox

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

Susan L. Makris[a,*,1,4], Howard M. Solomon[b,1,4], Ruth Clark[c,2,4], Kohei Shiota[d,3,4], Stephane Barbellion[e,2], Jochen Buschmann[f,2], Makoto Ema[g,3], Michio Fujiwara[h,3], Konstanze Grote[i,2], Keith P. Hazelden[j,1], Kok Wah Hew[k,1], Masao Horimoto[l,3], Yojiro Ooshima[m,3], Meg Parkinson[n,2], L. David Wise[o,1]

- Terminology of developmental anomalies (version 2)
- Published by Makris et al. 2009
- Changes necessary in the *Dev*Tox Nomenclature

| Diagnoses | External | Skeletal | Visceral | Maternal-Fetal |
|---|---|---|---|---|
| Number old | 151 | 467 | 277 | (2) |
| - delete | 38 | 11 | 17 | |
| - rename | 113 | 456 | 260 | 2 |
| - add | 54 | 567 | 273 | 17 |
| Number new | 167 | 1023 | 533 | 19 |



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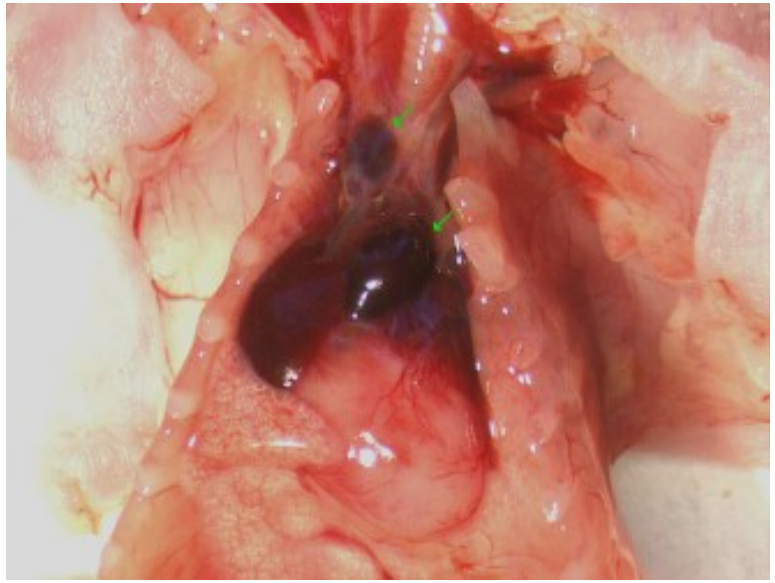
# Changes in Terminology

- Example: Visceral findings

| Old No. | Local. | Finding | New No. | Localization | Finding | |
|---|---|---|---|---|---|---|
| 3.1005.5040 | Aortic arch | Atresia | 3.1005.5040 | Aortic arch | Atretic | Image |
| 3.1005.5072 | Aortic arch | Dilated | 3.1005.5072 | Aortic arch | Dilated | Image |
| 3.1047.5008 | Heart | Absent left A-V valve | 3.1179.5002 | Left A-V valve | Absent | |
| 3.1047.5094 | Heart | Enlarged left A-V valve | 3.1179.5088 | Left A-V valve | Large | |
| 3.1047.5175 | Heart | Misshapen left A-V valve | 3.1179.5172 | Left A-V valve | Misshapen | |
| 3.1047.5216 | Heart | Small left A-V valve | 3.1179.5211 | Left A-V valve | Small | |
| 3.1047.5008 | Heart | Enlarged atrial chamber | 3.1173.5088 | Atrium | Large | Image |
| | | | 3.1173.5172 | Atrium | Misshapen | |
| | | | 3.1173.5211 | Atrium | Small | |

# *Dev*Tox Images

- Example: Atrium – Large



3.1047.5091-1-02 (old)

3.1173.5088-1-02 (new)

consecutive number

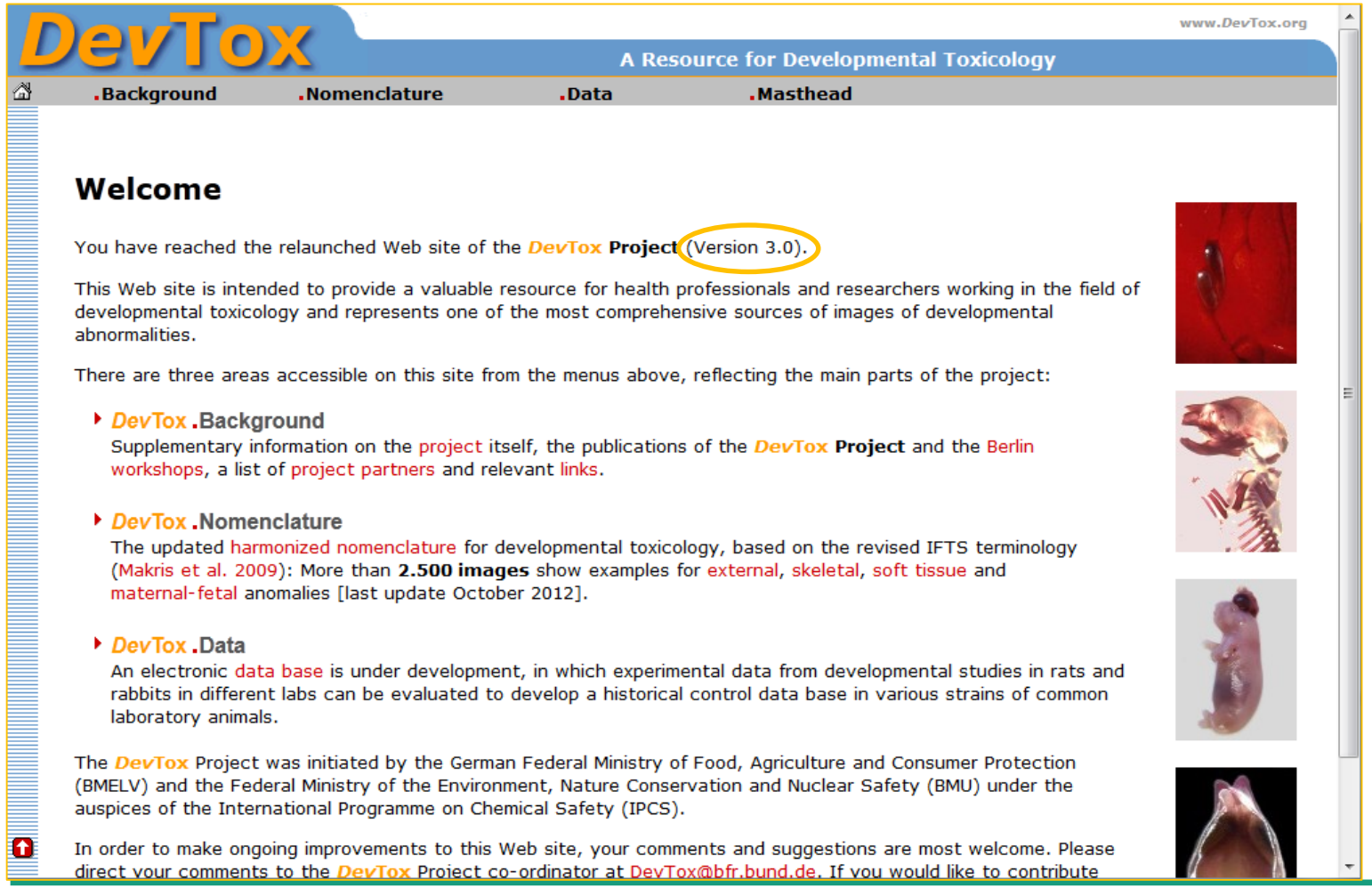
species: Rat

observation: Large

localization: Atrium

category: Visceral findings

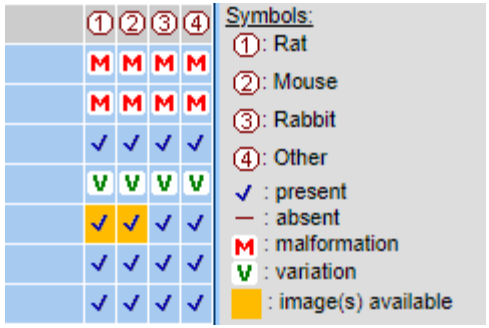
# *Dev*Tox Version 3 (2012)




- Launched on August 16, 2012
- New nomenclature
  - Maternal-fetal category
- Additional species / images
  - Hamster
  - Primate
  - Bird
- >2500 images
  - incl. post-natal images

# Selection Lists for Anomalies in *Dev*Tox

Pre-2012




| Mandible | Mandible 2016 | ① | ② | ③ | ④ | ⑤ | ⑥ | ⑦ | ⑧ | ⑨ |
|---|---|---|---|---|---|---|---|---|---|---|
| Absent | Absent | | | | | | | | | |
| Bent | Bent | | | | | | | | | |
| Fused | Fused | | | | | ✓ | | | | |
| Hole | Hole | | | | | | | | | |
| Incomplete ossification | Incomplete ossification | ✓ | | | | | | | | |
| Increased ossification | Increased ossification | | | | | | | | | |
| Isolated ossification site | Isolated ossification site | | | | | | | | | |
| Large | Large | | | | | | | | | |
| Long | Long | | | | | | | | | |
| Malpositioned | Malpositioned | | | | | | | | | |
| Misaligned | Misaligned | | | | | | | | | |
| Misshapen | Misshapen | | | ✓ | | | | | | |
| Short | Short | ✓ | | | | ✓ | | | | ✓ |
| Single incisor socket | Single incisor socket | | | | | | | | | |
| Small | Small | ✓ | | ✓ | | | | | | |
| Splayed | Splayed | | | | | | | | | |
| Supernumerary | Supernumerary | | | | | | | | | |
| Supernumerary site | Supernumerary site | | | | | | | | | |
| Thick | Thick | | | | | | | | | |
| Thin | Thin | | | | | | | | | |
| Unossified | Unossified | | | | | | | | | |
| Unossified area | Unossified area | | | | | | | | | |

According to:

Survey in 2013

Workshop 2014

Symbols:
①: Rat (Ra)
②: Mouse (Mo)
③: Rabbit (Rb)
④: Hamster (Ha)
⑤: Primate (Pr)
⑥: Guinea Pig (Gp)
⑦: Minipig (Mp)
⑧: Dog (Do)
⑨: Bird (Bi)
— : absent in species
: malformation
: grey zone
: variation
✓ : image(s) available
P : post-natal image(s) available



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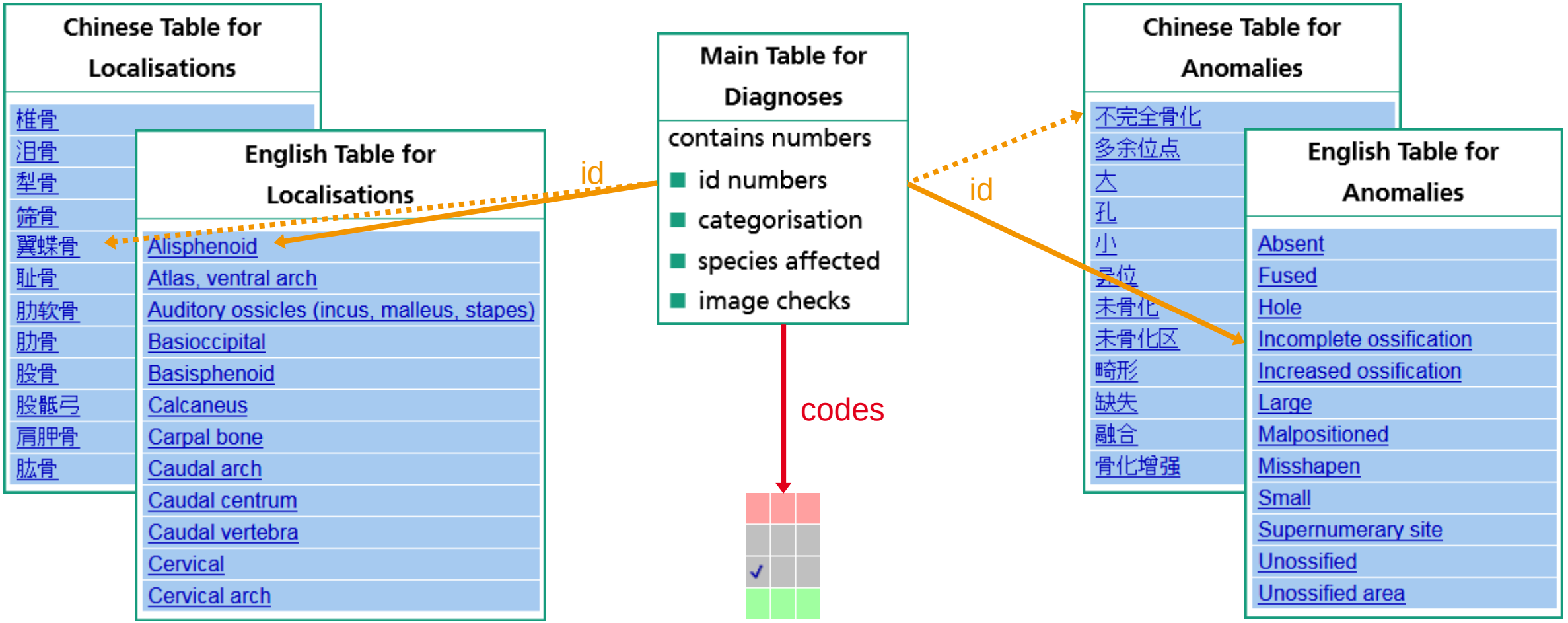
# Translation of *DevTox*

Translation into Chinese

- Proposal / templates in 2014
- Translation in China (Dr. Weihua Li)
  - Shanghai Institute of Planned Parenthood Research
  - WHO Collaboration Centre for Research in Human Reproduction
  - Fudan University
- Final checks at BfR (Dr. Wenna Xu)

- Release to the public on October 28, 2016

# Internal Structure of the Database



# New Abstraction Level

**Reduction of the variety of text sources**

Original English version

- Text files (HTML)
- PHP program scripts (Server)
- Database tables
- JavaScript programs (Browser: Menus)
- Button icons with info

Modified English version

- Text files (PHP)
- Database tables

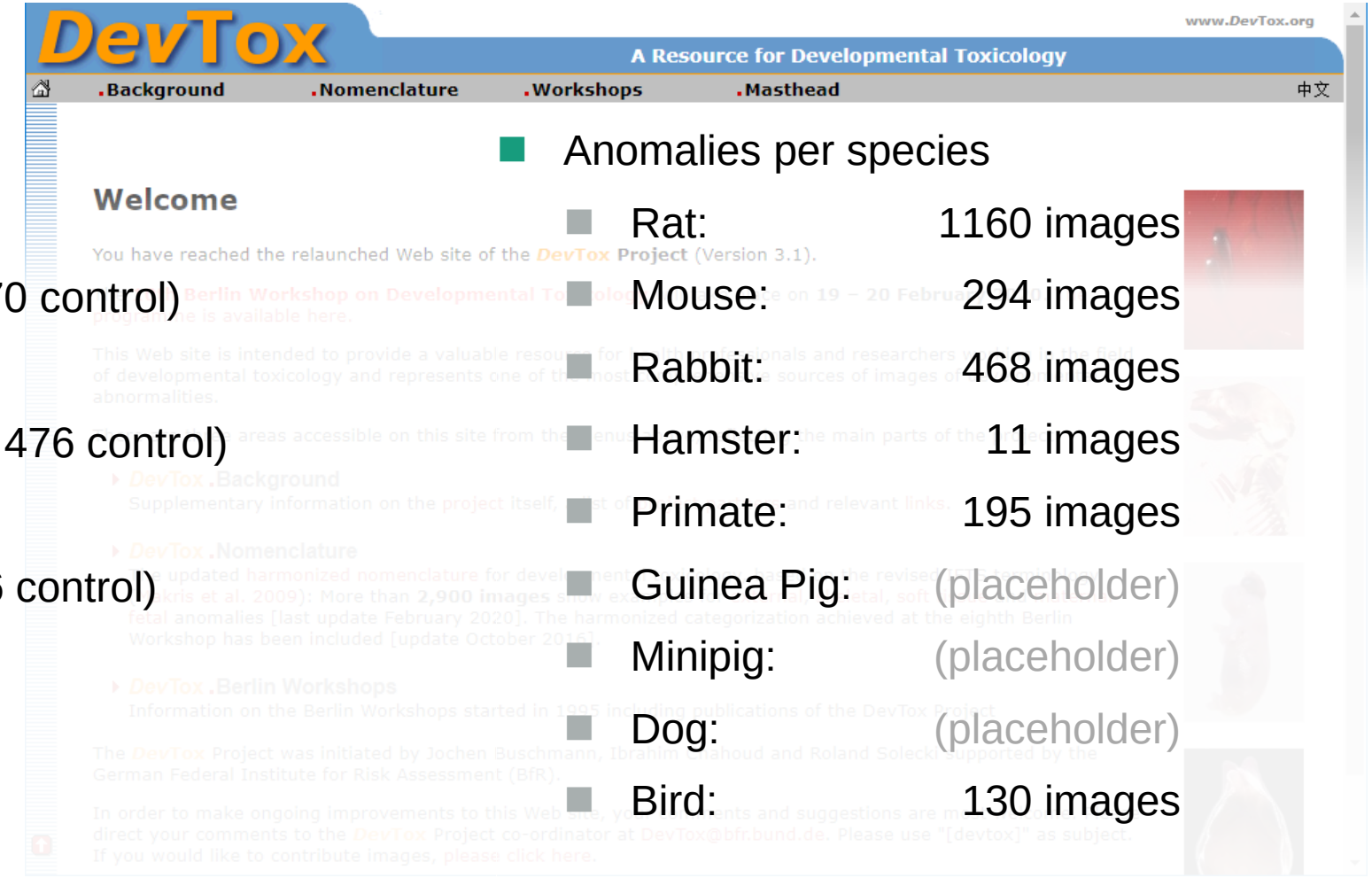
Can be applied to other languages

Chinese, …

# *Dev*Tox Version 3.1 (2020)

>2900 images:

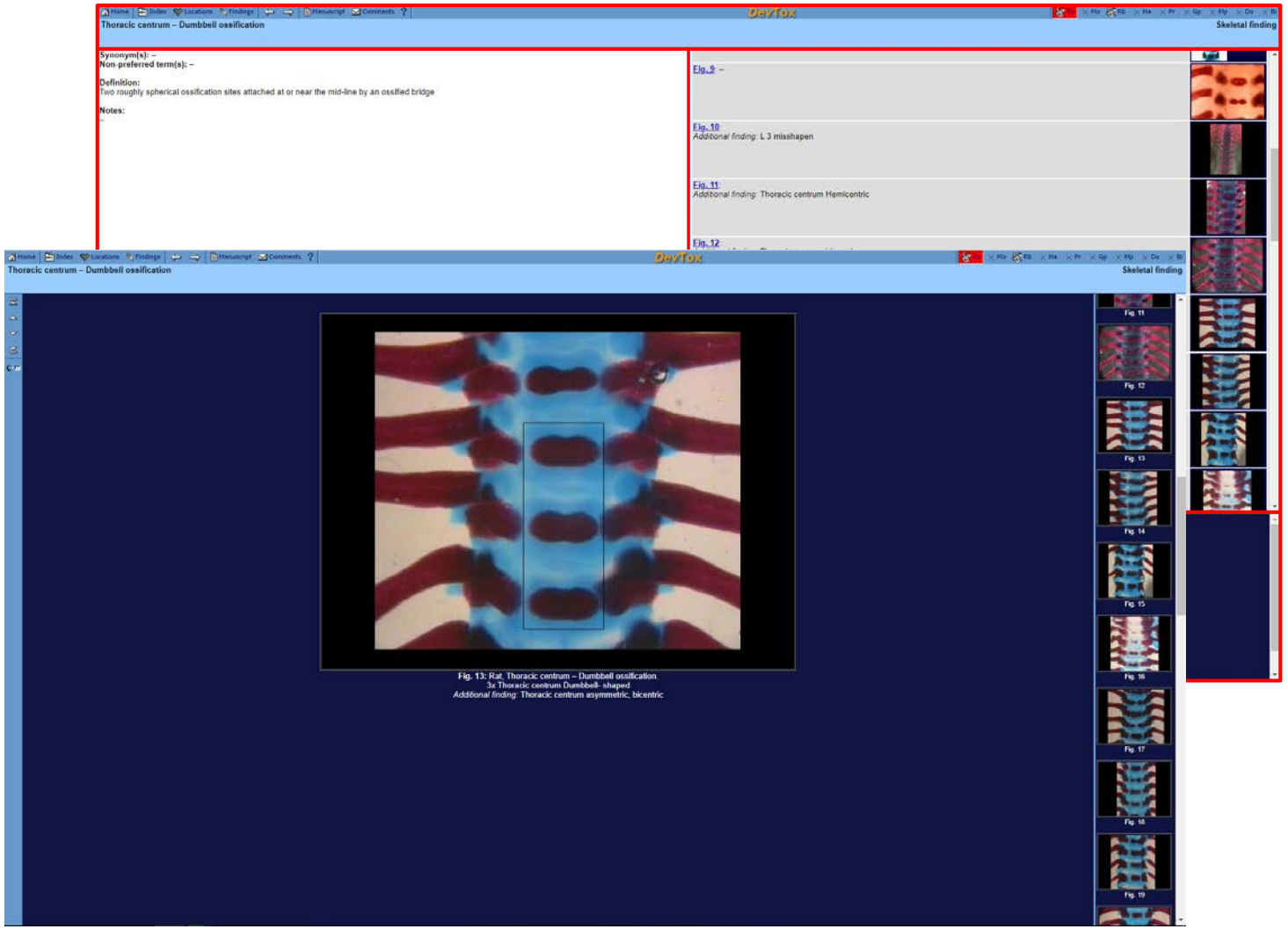
- External Findings
  - 678 images (508 anomalies, 170 control)
- Skeletal Findings
  - 1964 images (1488 anomalies, 476 control)
- Soft Tissue Findings
  - 308 images (262 anomalies, 46 control)




- Anomalies per species
  - Rat: 1160 images
  - Mouse: 294 images
  - Rabbit: 468 images
  - Hamster: 11 images
  - Primate: 195 images
  - Guinea Pig: (placeholder)
  - Minipig: (placeholder)
  - Dog: (placeholder)
  - Bird: 130 images

# *Dev*Tox Perspectives

- Current layout for 4:3 screens
  - Mode A: 800 x 600 pixel
  - Mode B: 1024 x 768 pixel
- Split into several frames




- Could be replaced by a modern layout

**Thank you for your attention!**

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