# ReProTect

**2004-2009**

**(www.reprotect.eu)**

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# Structure of the ReProTect Project

OpenTox Workshop, Potsdam, May 30, 2011

Bayer HealthCare
Bayer Schering Pharma

EggCentris
Center of Excellence for Reproductive Function Testing

Istituto Sperimentale Italiano
"Lazzaro Spallanzani"

IT University of Copenhagen

Imperial College

EBERHARD KARLS

# 33 partners

from Academia, Industry, SMEs and Governmental Institutes

BDS
BioDetection Systems

Vrije Universiteit Brussel

vito
vision on technology

Universität Konstanz

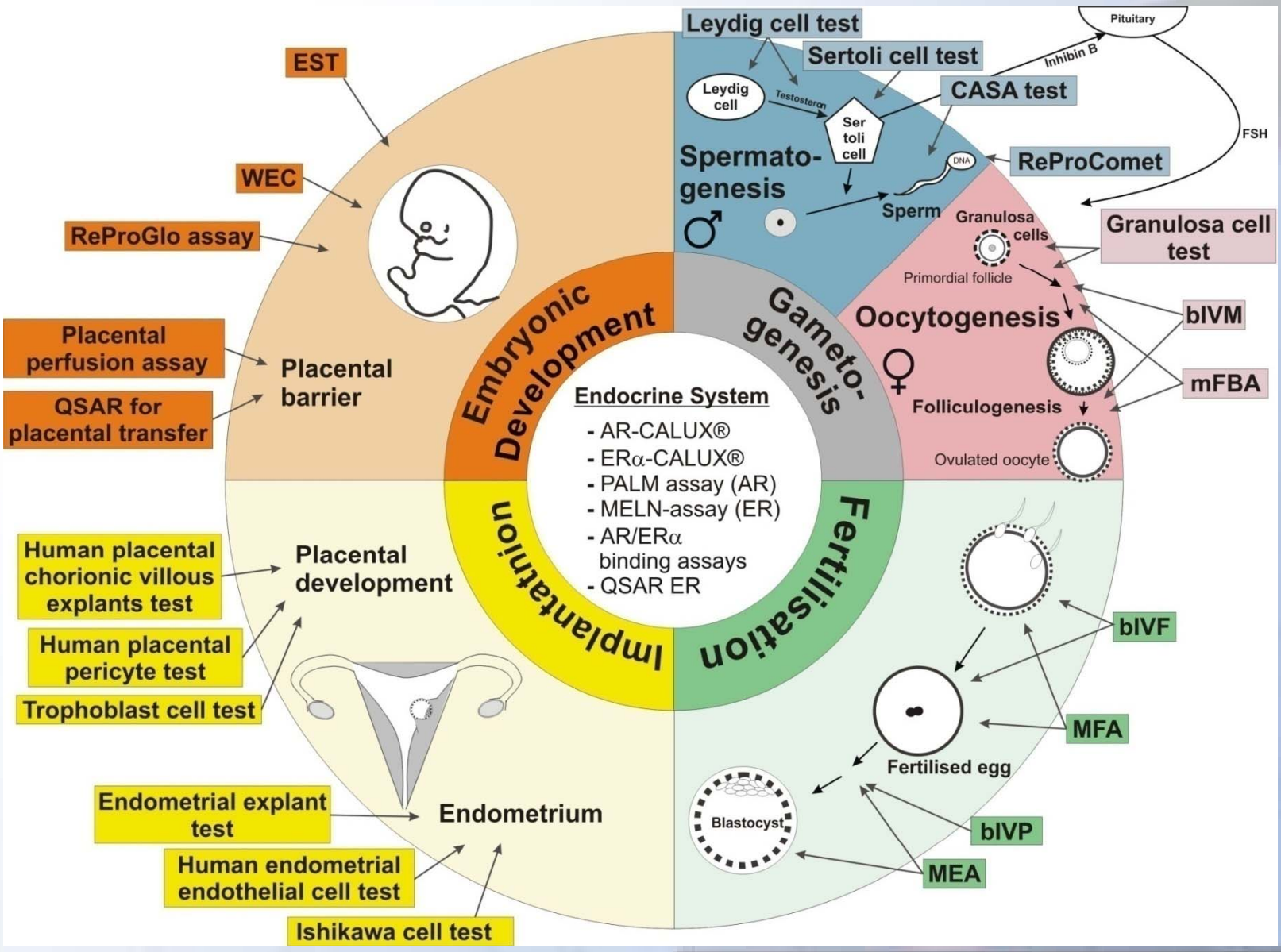
ProteoSys
Innovation in Functional Proteomics

Johnson&Johnson
PHARMACEUTICAL RESEARCH & DEVELOPMENT

UPPSALA UNIVERSITET

# Specific endpoints in the reproductive cycle





# Example: The ReProTect Feasibility Study



~150 ReProTect chemicals

Selection of 10 chemicals by independent experts

Selection criteria:

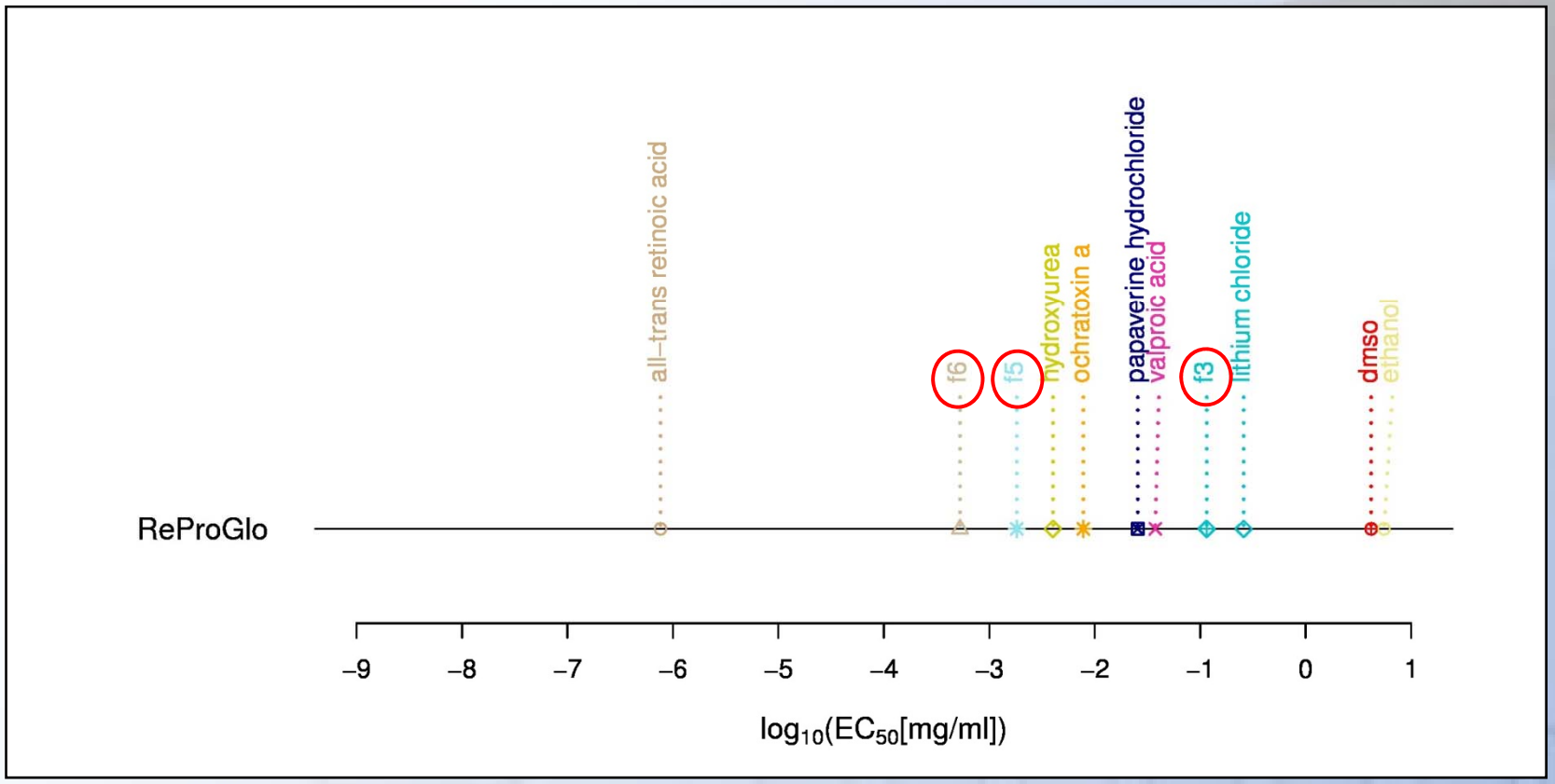
- *In vivo* effects well characterized
- No metabolic activation (CYP450-mediated) required

**Blinding** of chemicals (chemical 1,2,3,...10) and distribution to the experimental groups

Determination of $EC_{50}$- (or equivalent) values for all 10 chemicals in each of the assays

# The ReProTect Feasibility Study

OpenTox Workshop, Potsdam, May 30, 2011




- Nearest neighbor analysis (Prediction models, if available, were NOT used)
- Weight of evidence approach

# The ReProTect Feasibility Study

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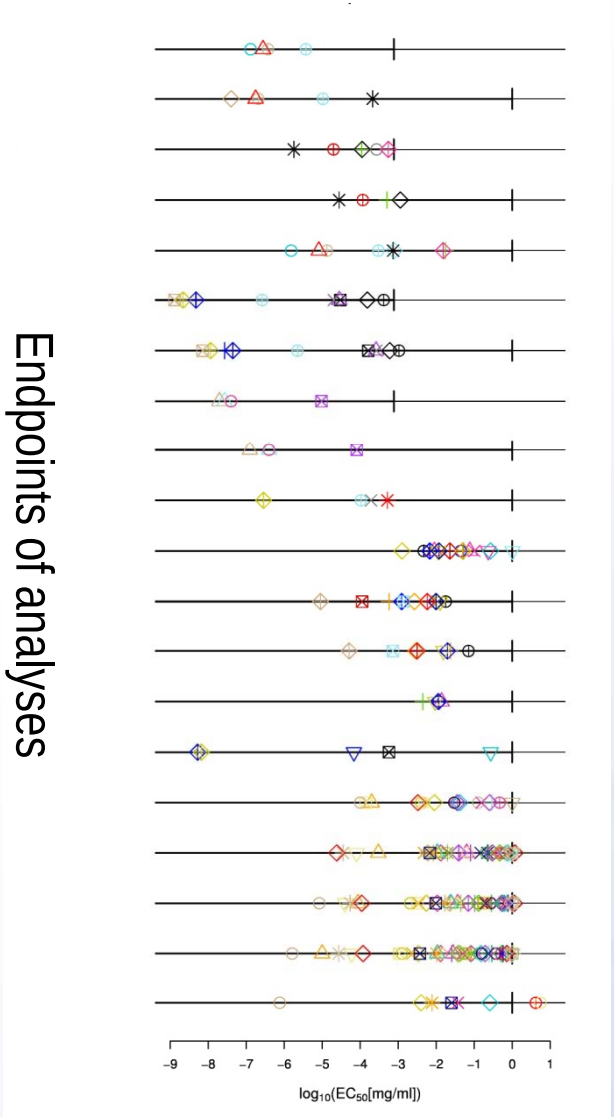
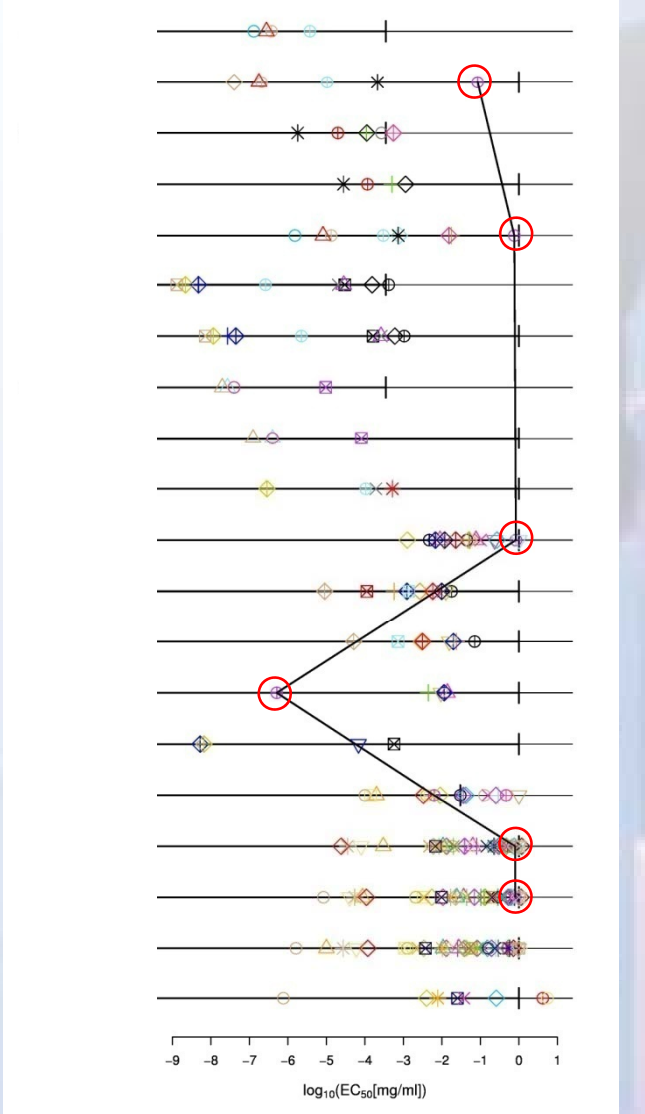
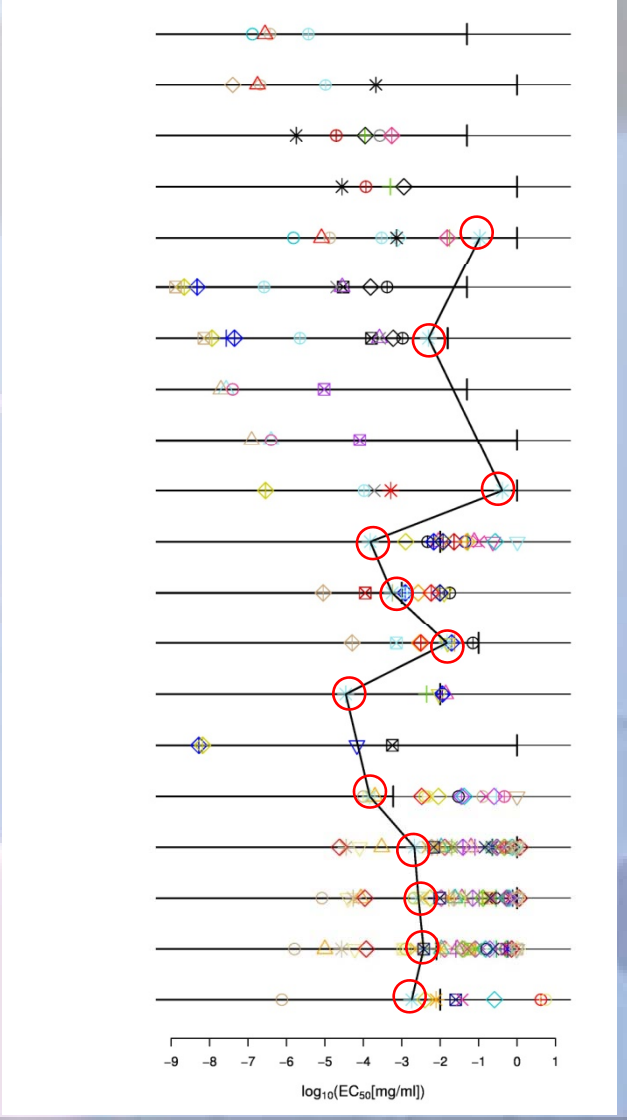
Compound 4

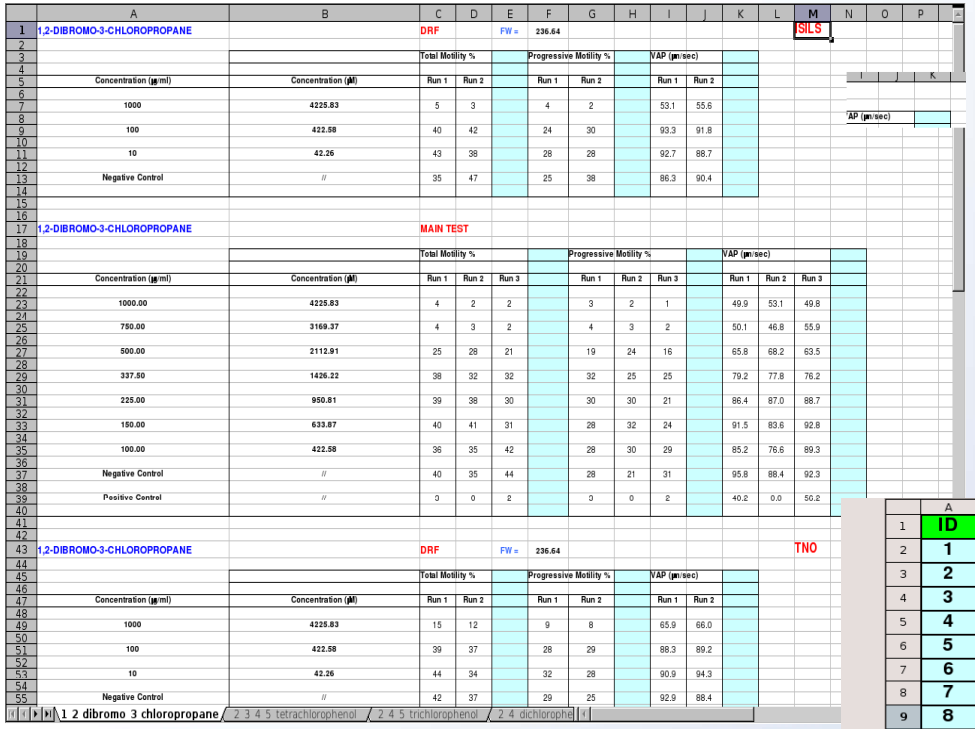



Compound 2




Compound 5





| | A | B | C | D | E | F | G | H | I | J | K | L | M | N | O | P |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 1,2-DIBROMO-3-CHLOROPROPANE | | DRF | | FW = | 236.64 | | | | | | | ISILS | | | |
| 2 | | | | | | | | | | | | | | | | |
| 3 | | | Total Motility % | | | Progressive Motility % | | | VAP (µm/sec) | | | | | | | |
| 4 | | | | | | | | | | | | | | | | |
| 5 | Concentration (µg/ml) | Concentration (µM) | Run 1 | Run 2 | | Run 1 | Run 2 | | Run 1 | Run 2 | | | | | | |
| 6 | | | | | | | | | | | | | | | | |
| 7 | 1000 | 4225.83 | 5 | 3 | | 4 | 2 | | 53.1 | 55.6 | | | | | | |
| 8 | | | | | | | | | | | | | | | | |
| 9 | 100 | 422.58 | 40 | 42 | | 24 | 30 | | 93.3 | 91.8 | | | | | | |
| 10 | | | | | | | | | | | | | | | | |
| 11 | 10 | 42.26 | 43 | 38 | | 28 | 28 | | 92.7 | 88.7 | | | | | | |
| 12 | | | | | | | | | | | | | | | | |
| 13 | Negative Control | // | 35 | 47 | | 25 | 38 | | 86.3 | 90.4 | | | | | | |
| 14 | | | | | | | | | | | | | | | | |
| 15 | | | | | | | | | | | | | | | | |
| 16 | | | | | | | | | | | | | | | | |
| 17 | 1,2-DIBROMO-3-CHLOROPROPANE | | MAIN TEST | | | | | | | | | | | | | |
| 18 | | | | | | | | | | | | | | | | |
| 19 | | | Total Motility % | | | | Progressive Motility % | | | VAP (µm/sec) | | | | | | |
| 20 | | | | | | | | | | | | | | | | |
| 21 | Concentration (µg/ml) | Concentration (µM) | Run 1 | Run 2 | Run 3 | | Run 1 | Run 2 | Run 3 | Run 1 | Run 2 | Run 3 | | | | |
| 22 | | | | | | | | | | | | | | | | |
| 23 | 1000.00 | 4225.83 | 4 | 2 | 2 | | 3 | 2 | 1 | 49.9 | 53.1 | 49.8 | | | | |
| 24 | | | | | | | | | | | | | | | | |
| 25 | 750.00 | 3169.37 | 4 | 3 | 2 | | 4 | 3 | 2 | 50.1 | 46.8 | 55.9 | | | | |
| 26 | | | | | | | | | | | | | | | | |
| 27 | 500.00 | 2112.91 | 25 | 28 | 21 | | 19 | 24 | 16 | 65.8 | 68.2 | 63.5 | | | | |
| 28 | | | | | | | | | | | | | | | | |
| 29 | 337.50 | 1426.22 | 38 | 32 | 32 | | 32 | 25 | 25 | 79.2 | 77.8 | 76.2 | | | | |
| 30 | | | | | | | | | | | | | | | | |
| 31 | 225.00 | 950.81 | 39 | 38 | 30 | | 30 | 30 | 21 | 86.4 | 87.0 | 88.7 | | | | |
| 32 | | | | | | | | | | | | | | | | |
| 33 | 150.00 | 633.87 | 40 | 41 | 31 | | 28 | 32 | 24 | 91.5 | 83.6 | 92.8 | | | | |
| 34 | | | | | | | | | | | | | | | | |
| 35 | 100.00 | 422.58 | 36 | 35 | 42 | | 28 | 30 | 29 | 85.2 | 76.6 | 89.3 | | | | |
| 36 | | | | | | | | | | | | | | | | |
| 37 | Negative Control | // | 40 | 35 | 44 | | 28 | 21 | 31 | 95.8 | 88.4 | 92.3 | | | | |
| 38 | | | | | | | | | | | | | | | | |
| 39 | Positive Control | // | 0 | 0 | 2 | | 0 | 0 | 2 | 40.2 | 0.0 | 50.2 | | | | |
| 40 | | | | | | | | | | | | | | | | |
| 41 | | | | | | | | | | | | | | | | |
| 42 | | | | | | | | | | | | | | | | |
| 43 | 1,2-DIBROMO-3-CHLOROPROPANE | | DRF | | FW = | 236.64 | | | | | | | TNO | | | |
| 44 | | | | | | | | | | | | | | | | |
| 45 | | | Total Motility % | | | Progressive Motility % | | | VAP (µm/sec) | | | | | | | |
| 46 | | | | | | | | | | | | | | | | |
| 47 | Concentration (µg/ml) | Concentration (µM) | Run 1 | Run 2 | | Run 1 | Run 2 | | Run 1 | Run 2 | | | | | | |
| 48 | | | | | | | | | | | | | | | | |
| 49 | 1000 | 4225.83 | 15 | 12 | | 9 | 8 | | 65.9 | 66.0 | | | | | | |
| 50 | | | | | | | | | | | | | | | | |
| 51 | 100 | 422.58 | 39 | 37 | | 28 | 29 | | 88.3 | 89.2 | | | | | | |
| 52 | | | | | | | | | | | | | | | | |
| 53 | 10 | 42.26 | 44 | 34 | | 32 | 28 | | 90.9 | 94.3 | | | | | | |
| 54 | | | | | | | | | | | | | | | | |
| 55 | Negative Control | // | 42 | 37 | | 29 | 25 | | 92.9 | 88.4 | | | | | | |

1 2 dibromo 3 chloropropane | 2 3 4 5 tetrachlorophenol | 2 4 5 trichlorophenol | 2 4 dichlorophe

Present: Partners design their own templates:
Data storage AND presentation

ReProTect: Extract data with
Perl or Python scripts for
statistical analysis

Future: Each template with
individual data export routine
(e.g. VBA in MS Excel)

Export in standardized formats

| | A | B | C | D | E | F | G | H | I | J | K | L |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | ID | Laboratory | Substance | Vehicle | Batch | Dose | Run | TM | TM Unit | PM | PM Unit | VAP |
| 2 | 1 | ISILS | 1,2-DIBROMO-3-CHLOROPROPANE | Acetone | C | 0.000 | 1 | 35 | % | 25 | % | 86.3 |
| 3 | 2 | ISILS | 1,2-DIBROMO-3-CHLOROPROPANE | Acetone | C | 0.000 | 2 | 47 | % | 38 | % | 90.4 |
| 4 | 3 | ISILS | 1,2-DIBROMO-3-CHLOROPROPANE | Acetone | C | 10.000 | 1 | 43 | % | 28 | % | 92.7 |
| 5 | 4 | ISILS | 1,2-DIBROMO-3-CHLOROPROPANE | Acetone | C | 10.000 | 2 | 38 | % | 28 | % | 88.7 |
| 6 | 5 | ISILS | 1,2-DIBROMO-3-CHLOROPROPANE | Acetone | C | 100.000 | 1 | 40 | % | 24 | % | 93.3 |
| 7 | 6 | ISILS | 1,2-DIBROMO-3-CHLOROPROPANE | Acetone | C | 100.000 | 2 | 42 | % | 30 | % | 91.8 |
| 8 | 7 | ISILS | 1,2-DIBROMO-3-CHLOROPROPANE | Acetone | C | 1000.000 | 1 | 5 | % | 4 | % | 53.1 |
| 9 | 8 | ISILS | 1,2-DIBROMO-3-CHLOROPROPANE | Acetone | C | 1000.000 | 2 | 3 | % | 2 | % | 55.6 |
| 10 | 9 | ISILS | 1,2-DIBROMO-3-CHLOROPROPANE | Acetone | C | 0.000 | 1 | 40 | % | 28 | % | 95.8 |
| 11 | 10 | ISILS | 1,2-DIBROMO-3-CHLOROPROPANE | Acetone | C | 0.000 | 2 | 35 | % | 21 | % | 88.4 |
| 12 | 11 | ISILS | 1,2-DIBROMO-3-CHLOROPROPANE | Acetone | C | 0.000 | 3 | 44 | % | 31 | % | 92.3 |
| 13 | 12 | ISILS | 1,2-DIBROMO-3-CHLOROPROPANE | Acetone | C | 100.000 | 1 | 36 | % | 28 | % | 85.2 |
| 14 | 13 | ISILS | 1,2-DIBROMO-3-CHLOROPROPANE | Acetone | C | 100.000 | 2 | 35 | % | 30 | % | 76.6 |
| 15 | 14 | ISILS | 1,2-DIBROMO-3-CHLOROPROPANE | Acetone | C | 100.000 | 3 | 42 | % | 29 | % | 89.3 |
| 16 | 15 | ISILS | 1,2-DIBROMO-3-CHLOROPROPANE | Acetone | C | 150.000 | 1 | 40 | % | 28 | % | 91.5 |
| 17 | 16 | ISILS | 1,2-DIBROMO-3-CHLOROPROPANE | Acetone | C | 150.000 | 2 | 41 | % | 32 | % | 83.6 |
| 18 | 17 | ISILS | 1,2-DIBROMO-3-CHLOROPROPANE | Acetone | C | 150.000 | 3 | 31 | % | 24 | % | 92.8 |
| 19 | 18 | ISILS | 1,2-DIBROMO-3-CHLOROPROPANE | Acetone | C | 225.000 | 1 | 39 | % | 30 | % | 86.4 |
| 20 | 19 | ISILS | 1,2-DIBROMO-3-CHLOROPROPANE | Acetone | C | 225.000 | 2 | 38 | % | 30 | % | 87.0 |
| 21 | 20 | ISILS | 1,2-DIBROMO-3-CHLOROPROPANE | Acetone | C | 225.000 | 3 | 30 | % | 21 | % | 88.7 |
| 22 | 21 | ISILS | 1,2-DIBROMO-3-CHLOROPROPANE | Acetone | C | 337.500 | 1 | 38 | % | 32 | % | 79.2 |
| 23 | 22 | ISILS | 1,2-DIBROMO-3-CHLOROPROPANE | Acetone | C | 337.500 | 2 | 32 | % | 25 | % | 77.8 |
| 24 | 23 | ISILS | 1,2-DIBROMO-3-CHLOROPROPANE | Acetone | C | 337.500 | 3 | 32 | % | 25 | % | 76.2 |
| 25 | 24 | ISILS | 1,2-DIBROMO-3-CHLOROPROPANE | Acetone | C | 500.000 | 1 | 25 | % | 19 | % | 65.8 |
| 26 | 25 | ISILS | 1,2-DIBROMO-3-CHLOROPROPANE | Acetone | C | 500.000 | 2 | 28 | % | 24 | % | 68.2 |
| 27 | 26 | ISILS | 1,2-DIBROMO-3-CHLOROPROPANE | Acetone | C | 500.000 | 3 | 21 | % | 16 | % | 63.5 |

Ganzer Bildschirm

Data | Preferences

# The ReProTect database

OpenTox Workshop, Potsdam, May 30, 2011

Server: localhost ▸ Datenbank: ReProTect

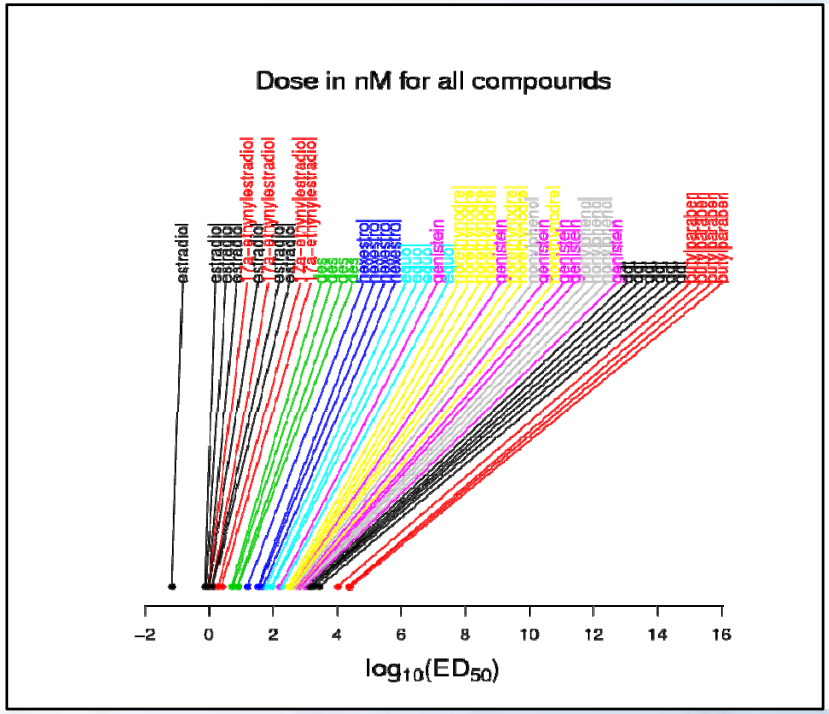
Struktur | SQL | Suche | Abfrageeditor | Exportieren | Importieren | Operationen | Rechte | Löschen

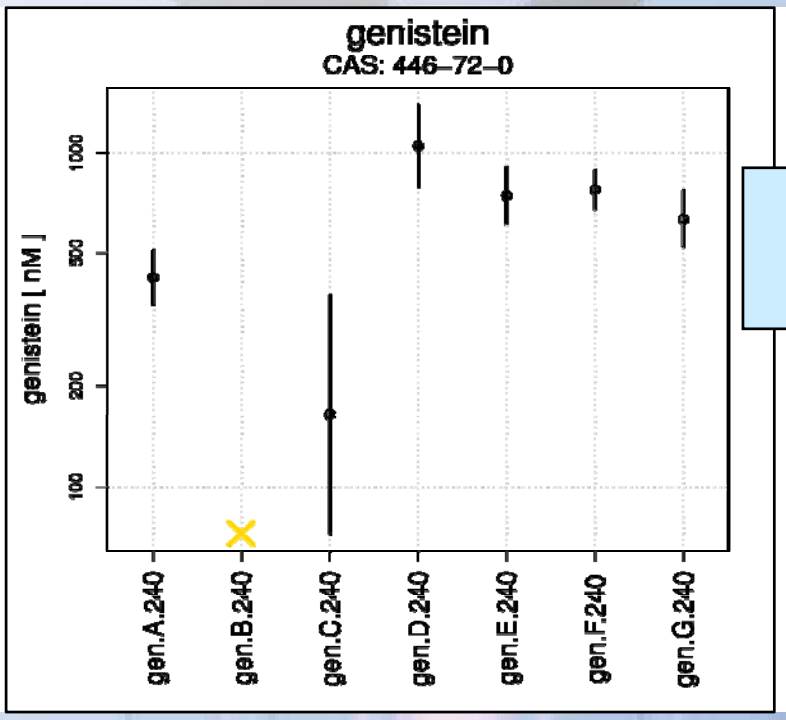
| | Tabelle | Aktion | Einträge | Typ | Kollation | Größe | Überhang |
|---|---|---|---|---|---|---|---|
| ☐ | Assay | | ~28 | InnoDB | utf8_general_ci | 48,0 KiB | - |
| ☐ | CompoundHarm | | ~128 | InnoDB | utf8_general_ci | 64,0 KiB | - |
| ☐ | CompoundInd | | ~155 | InnoDB | utf8_general_ci | 32,0 KiB | - |
| ☐ | DoseUnit | | ~6 | InnoDB | utf8_general_ci | 32,0 KiB | - |
| ☐ | ED50 | | ~890 | InnoDB | utf8_general_ci | 96,0 KiB | - |
| ☐ | Endpoint | | ~25 | InnoDB | utf8_general_ci | 32,0 KiB | - |
| ☐ | Lab | | ~15 | InnoDB | utf8_general_ci | 16,0 KiB | - |
| ☐ | Run | | ~1,522 | InnoDB | utf8_general_ci | 336,0 KiB | - |
| ☐ | Target | | ~7 | InnoDB | utf8_general_ci | 16,0 KiB | - |
| ☐ | Treatment | | ~338 | InnoDB | utf8_general_ci | 96,0 KiB | - |
| ☐ | WarningsHarm | | ~8 | InnoDB | utf8_general_ci | 32,0 KiB | - |
| ☐ | WarningsInd | | ~632 | InnoDB | utf8_general_ci | 96,0 KiB | - |
| | 12 Tabellen | Gesamt | ~3,754 | MyISAM | latin1_swedish_ci | 896,0 KiB | 0 Bytes |

Alle auswählen / Auswahl entfernen markierte:

| GlobalID | Assay | Target | Endpoint | Lab | Compound | CAS | Run | ED50 |
|---|---|---|---|---|---|---|---|---|
| 670 | | 6 | Standard | | genistein | 446-72-0 | gen.A.240 | 422.6 |
| 672 | | 6 | Standard | | genistein | 446-72-0 | gen.C.240 | 164.5 |
| 673 | | 6 | Standard | | genistein | 446-72-0 | gen.D.240 | 1049.0 |
| 674 | | 6 | Standard | | genistein | 446-72-0 | gen.E.240 | 744.5 |
| 675 | | 6 | Standard | | genistein | 446-72-0 | gen.F.240 | 776.4 |
| 676 | | 6 | Standard | | genistein | 446-72-0 | gen.G.240 | 633.1 |

| Lower | Upper | DoseUnit | MW | CompoundHarm | CompoundRef | RefED50 | RefDoseUnit |
|---|---|---|---|---|---|---|---|
| 350.2 | 509.9 | nM | 270.2369 | genistein | genistein | 4.226e-07 | M |
| 72.5 | 373.4 | nM | 270.2369 | genistein | genistein | 1.645e-07 | M |
| 788.8 | 1394.0 | nM | 270.2369 | genistein | genistein | 1.049e-06 | M |
| 611.3 | 906.6 | nM | 270.2369 | genistein | genistein | 7.445e-07 | M |
| 678.6 | 888.4 | nM | 270.2369 | genistein | genistein | 7.764e-07 | M |
| 520.1 | 770.7 | nM | 270.2369 | genistein | genistein | 6.331e-07 | M |




~150 compounds

# Description and Evaluation of *in vivo Data on Fertility and Developmental Toxicity*

OpenTox Workshop, Potsdam, May 30, 2011

## 58) Cadmium chloride [7790-78-5]

| 58 | Mode of action | Male Fertility | | Female Fertility | | Developmental Toxicity | |
|---|---|---|---|---|---|---|---|
| **Cadmium chloride [7790-78-5]** | **genotoxic, carcinogenic, general toxicant** | + | impaired fertility (10 mg/kg bw) | + | impaired fertility, sterility (≥5 mg/kg bw) | + | teratogenic in rats (20 mg/kg bw, orally) and mice, postnatal behavioural impairment (>0.4 mg/kg bw) |

**Mode of Action**

Cadmium is a carcinogenic, DNA-reactive general toxicant (ReProTect 2008 b).

**Male Fertility**

Four groups of Sprague-Dawley rats, each of which consisted of 14 males and 14 females, were administered 0, 0.1, 1.0 and 10.0 mg/kg/day of cadmium (Cd) for 6 weeks. Numbers of total implants and live fetuses in the 1.0 mg/kg group decreased slightly, but there was no significant difference from the control. Numbers of total implantations and live fetuses decreased significantly in the 10.0 mg/kg group. In this group, the number of resorbed fetuses increased significantly and the number of corpora lutea decreased without showing a significant difference from the control. Fetuses from the 10.0 mg/kg group showed decreased body weight, body length, and tail length and increased placental weight. About one-third of fetuses were subjected to visceral examination, but no specific anomalies considered to be due to Cd toxicity were found. Skeletal examination was performed for the remaining two-thirds of the fetuses. Delayed ossification of the sternebrae and caudal vertebrae was observed. No dominant lethality was found under the conditions used here. Although physiological deterioration caused by 10.0 mg/kg of Cd has an adverse effect on mating performance, mating ratio, the number of total implants, the number of live fetuses, and the ossification of fetuses, Cd induced neither teratogenicity nor dominant lethality (Sutou et al. 1980).

Effects of a single subcutaneous injection of 1 or 5 mg/rat of cadmium chloride ($CdCl_2$) on circulating steroids and fertility were studied over a period of 120 days in fertile male rats. Androgens and fertility returned to normal 120 days after 1 mg $CdCl_2$ but males treated with 5 mg showed none to poor restoration of some of these parameters. The in vitro release of testosterone (T), 5 alpha-dihydrotestosterone (5 alpha-DHT) and androstenedione (delta 4A) by the decapsulated tests from $CdCl_2$ treated males was significantly reduced whereas progesterone (delta 4P) was accumulated in significantly higher amounts into the incubation medium. When testes from $CdCl_2$ treated males were incubated in vitro with hCG, a dose and time dependent stimulation of steroidogenesis was evident. Since the testes regained the steroidogenic capacity but the males remained sterile 120 days after 5 mg $CdCl_2$ treatment, it appeared that $CdCl_2$ induced a permanent damage to the germinal components of the testes (Saksena and Lau, 1979; ReProTect 2008 b)

**Female Fertility**

Cadmium chloride was administered by gavage to female rats 5 days a week for 5 weeks, then during mating and gestation periods at doses of 0.04, 0.4, and 4 mg Cd/kg/day. Treatment with cadmium neither affected the survival and fertility of females, nor produced overt fetotoxic effects. Fetal cadmium concentration was not related to the level of exposure. Litter size, body weight gain and viability of offspring during 2 months after parturition were similar in all groups. The exploratory locomotor activity of 2-month-old males and females born to rats given 0.4 and 4 mg Cd/kg/day was significantly reduced. The progeny of cadmium-treated females showed decreased performance in the rotarod test. In general, the degree of behavioral impairment was dose-related (Baranski et aql. 1983).

Adult female rats having regular ovarian cycles were treated with 2.5, 5 or 10 mg/kg cadmium chloride ($CdCl_2$) during estrus or diestrus and mated 32, 80 or 132 h post-treatment. Sperm positivity was checked next day on the predicted estrus. Maternal effects during pregnancy, fetal outcome on day 10 or at term as well as postnatal development of the F-1 generation were recorded. $CdCl_2$ caused sterility in 40 or 87% of animals at doses 5 and 10 mg/kg, respectively. Influence of Cd on fertility depended on the day of the cycle, and on the time elapsed between treatment and mating. The Cd-caused overt toxicity in fertile female rats was expressed by dose-dependent decrease in maternal body weight gain and increased progesterone blood levels. No treatment-related alteration in number and weight of conception day 10 of pregnancy or in weight and size of litters, rate of males and females at term and during the 21-day post-parturition study could be seen. It is concluded that Cd given prior mating may lead to sterility in a dose-dependent fashion. This is suggested to be caused by anovulation resulting from reversible pituitary disfunction. Animals proving fertile in spite of Cd-treatment have developed tolerance against Cd in terms of fetal outcome and postnatal development (Paksy et al., 1996; ReProTect 2008 b);

The subcutaneous administration of cadmium chloride ($CdCl_2$) 24 h before hCG-induced ovulation in rabbits sacrificed 14 h after induction of ovulation leads to a dose-dependent decrease in the number of oviductal eggs and the number of eggs shed. While a dose of 1.25 mg/kg $CdCl_2$ imposed no effect, only 50-67% of the dogs treated with 2.5 or 5 mg/kg $CdCl_2$ ovulated and of those ovulated eggs 35.6 and 45%, respectively, were found in the oviducts. At a dose of 7.5 mg/kg $CdCl_2$, a higher proportion (57.1%) of the does failed to ovulate and only 16% of the eggs were recovered from the oviducts (Saksena, 1982; ReProTect 2008 b).

**Developmental Toxicity**

Cadmium is a well-known teratogen in laboratory animals (Padmanabhan and Hameed 1986).

In Wistar rats, the teratogenic dose was derived with 20 mg Cd/kg bw administered by the oral route during organogenesis from Day 6 to Day 14. To evaluate the long-term behavioral effect in offspring, a subteratogenic Cd dose applied orally during organogenesis (1) was not able to induce maternal toxicity; (2) induced external malformations; (3) increased significantly fetus anomalies and malformations, with reduced metacarpus ossification, cleft palate and right or left renal cavitation being observed in these animals; (4) did not modify pup body weight or weight gain during the lactation period; (5) improved testis descent and delayed the vaginal opening of pups; (6) did not modify ear unfolding, incisor eruption, eye opening, negative geotaxis or palmar grasp; (7) did not modify the open-field parameters and the stereotyped behavior of male or female pups; and (8) modified male sexual behavior and (9) reduced female sexual behaviour (Salvatori et al. 2004).

A teratological study was conducted in pregnant Sprague-Dawley rats dosed orally with diethylstilbestrol (DES), zeranol (ZN), 3,3',4,4'-tetrachlorobiphenyl (4CB), cadmium, or lead on days 6-18 of gestation. Fetuses were examined on day 19. Cadmium produced no malformations although incorporation of [3H]amino acids by limb cartilage was slightly increased (Wardell et al. 1982).

**References**


Barański B, Stetkiewicz I, Sitarek K, Szymczak W (1983) Effects of oral, subchronic cadmium administration on fertility, prenatal and postnatal progeny development in rats. Arch Toxicol. 1983 Dec;54(4):297-302

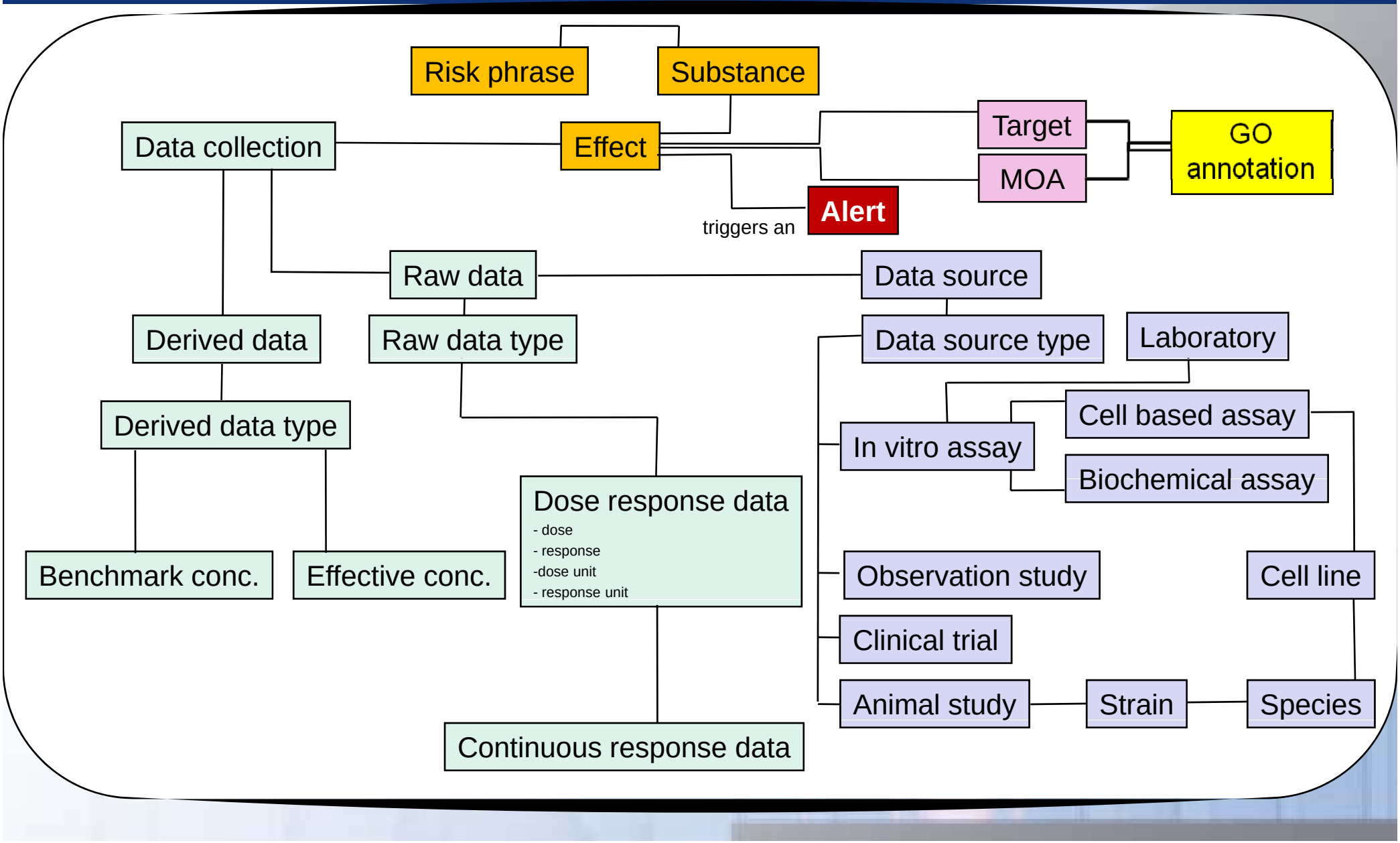
Salvatori F, Talassi CB, Salzgeber SA, Spinosa HS, Bernardi MM (2004) Embryotoxic and long-term effects of cadmium exposure during embryogenesis in rats. Neurotoxicol Teratol. 2004 Sep-Oct;26(5):673-80

Sutou S, Yamamoto K, Sendota H, Sugiyama M (1980) Toxicity, fertility, teratogenicity, and dominant lethal tests in rats administered cadmium subchronically. II. Fertility, teratogenicity, and dominant lethal tests. Ecotoxicol Environ Saf. 1980 Mar;4(1):51-6

Wardell RE, Seegmiller RE, Bradshaw WS (1982) Induction of prenatal toxicity in the rat by diethylstilbestrol, zeranol,3,4,3',4',-tetrachlorobiphenyl, cadmium, and lead. Teratology. 1982 Dec;26(3):229-37

# Entity Relationship Diagram





**Ontology:** A formal representation of the knowledge by a set of concepts within a domain and the relationships between those concepts.
It is used to reason about the properties of that domain, and may be used to describe the domain (Wikipedia).

**Example:** Glufosinate ammonium: Positive in MEPA

inhibits
- GO:0004356: glutamate-ammonia ligase activity (MF)
  Catalysis of the reaction: ATP + L-glutamate + NH3 = ADP + phosphate + L-glutamine.

interferes with
- GO:0001825: blastocyst formation (BP)
  The initial formation of a blastocyst from a solid ball of cells known as a morula.

interferes with
- GO:0001824: blastocyst development (BP)
  The process whose specific outcome is the progression of the blastocyst over time, from its formation to the mature structure. The mammalian blastocyst is a hollow ball of cells containing two cell types, the inner cell mass and the trophectoderm.