Alternative Testverfahren und intelligente Teststrategien

Position aus Sicht der BASF

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How flexible will REACH be?

STEP 2 – CONSIDER INFORMATION NEEDS

The registrant shall identify what information is required for the registration. First, the relevant Annex or Annexes to be followed shall be identified, according to tonnage. These Annexes set out the standard information requirements, but shall be considered in conjunction with Annex IX, which allows variation from the standard approach, where it can be justified.

Annex IV, Guidance Note

How flexible will REACH be?

In order to avoid unnecessary animal testing, testing on vertebrate animals for the purposes of this Regulation shall be undertaken only as a last resort.
It is also necessary to take measures limiting unnecessary duplication of other tests.

Article 23(1)

How flexible will REACH be?

Before new tests are carried out to determine the properties listed in this Annex, all available *in vitro* data, *in vivo* data, historical data, data from valid (Q)SARs and data from structurally related substances (read-across approach) shall be assessed first.

Annexes V - VIII

How flexible will REACH be?

If the results obtained from the use of such *in vitro* methods do not indicate a certain dangerous property, the relevant test shall nevertheless be carried out ...

Such confirmation may be waived, if the following conditions are met:

- results are derived from an in vitro, methods whose scientific validity has bee establsihed by a validation study according to internationally agreed validation principles

(2) results are adequate for the purpose of classification and labelling and risk assessment, and

(3) adequate and reliable documentation of the applied method is provided.

Annex IX 1.4.

Role of alternatives in REACH and Intelligent Testing?

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Intelligent Testing “Toolbox”

- Exposure-based waiving / testing
- Threshold of toxicological concern
- SARs and QSARs
- In vitro tests
- Read-across
- Optimised in vivo tests
- Tiered / Triggered testing

Role of alternatives in REACH and Intelligent Testing?

Intelligent Testing “Toolbox”

- Exposure-based waiving / testing

  ECETOC – Targeted Risk Assessment
  www.ecetoc-tra.org

2. Threshold of toxicological concern (TTC)

   TTC is a useful, exposure based, concept
   Individual end-point related TTCs may help to reduce testing – needs to be investigated

Role of alternatives in REACH and Intelligent Testing?

Intelligent Testing “Toolbox”

- SARs and QSARs

  Priorization: Yes

  For Risk Assessment & Classification:
  Only when quality & reliability criteria are met
  Accept positive & negative

- In vitro tests

The 3 Rs at BASF: Environment and Cooperations

- **The replacement of animal experiments is practiced by BASF wherever it is possible and reasonable (Sustainability report 2004).**
- **Since more than 20 years, BASF participates in all relevant research activities for the development of alternative methods.**

We cooperate with the following national and international organizations:

- **ZEBET**
  (Centre for Documentation and Evaluation of Alternatives to Animal Experiments)
- **ECVAM**
  (European Centre for the Validation of Alternative Methods)

In vitro / Alternative Methods performed by BASF

- EpiDerm™ (Skin Irritation)
- HET-CAM Test (Eye Irritation)
- Mouse Local Lymph Node Assay (Sensitization)
- Dermal Penetration
- SHE Assay
- New Developments

Refinement, Reduction, Replacement

- BASF follows a tiered approach for Skin and Eye Irritation testing (evaluation of available data, in vitro tests before animal testing)
- Non isolated intermediates are tested in vitro only
- The use of rabbits for skin and eye irritation testing is reduced by about 25%
- Using the LLNA as replacement of more invasive guinea pig tests reduces suffering of animals and provides additional concentration-response information
- In vitro dermal penetration data may be sufficient for risk assessment (no further in vivo testing)

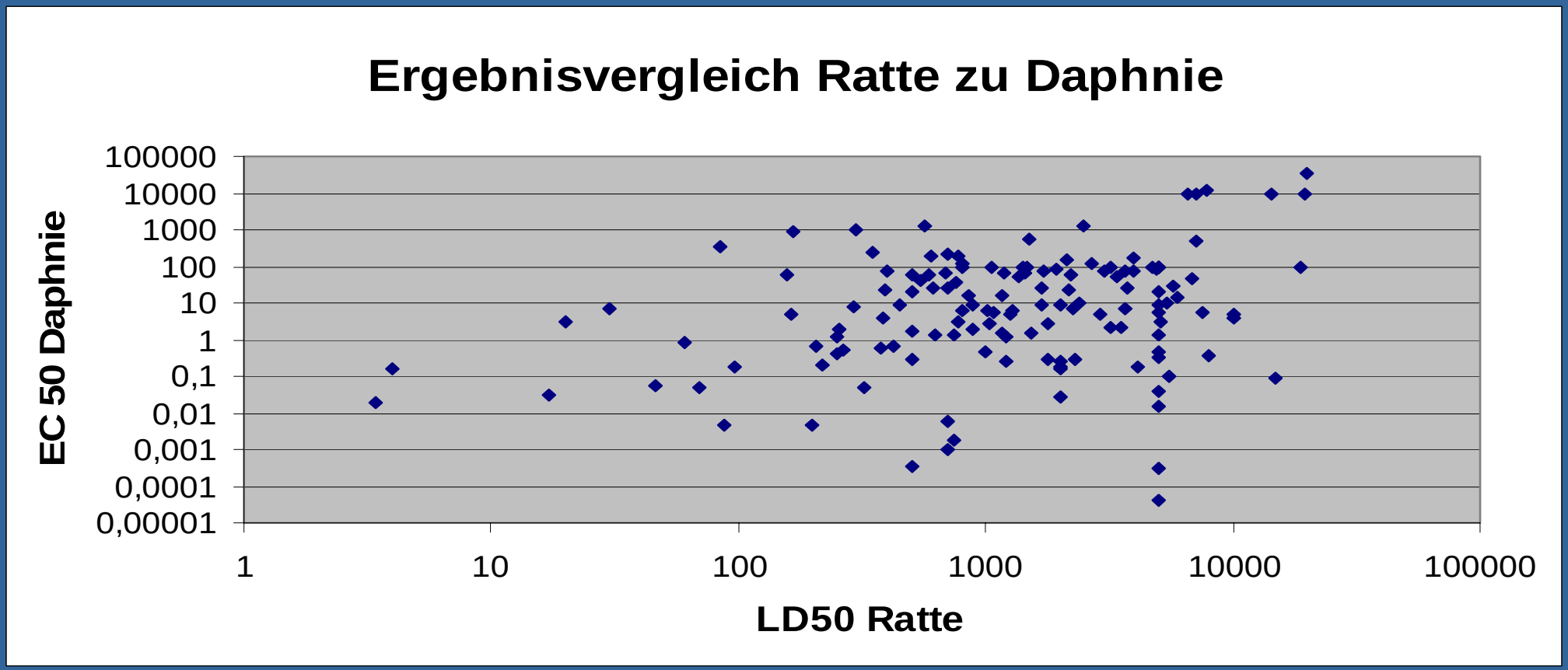
Alternative Methods at BASF

Objective

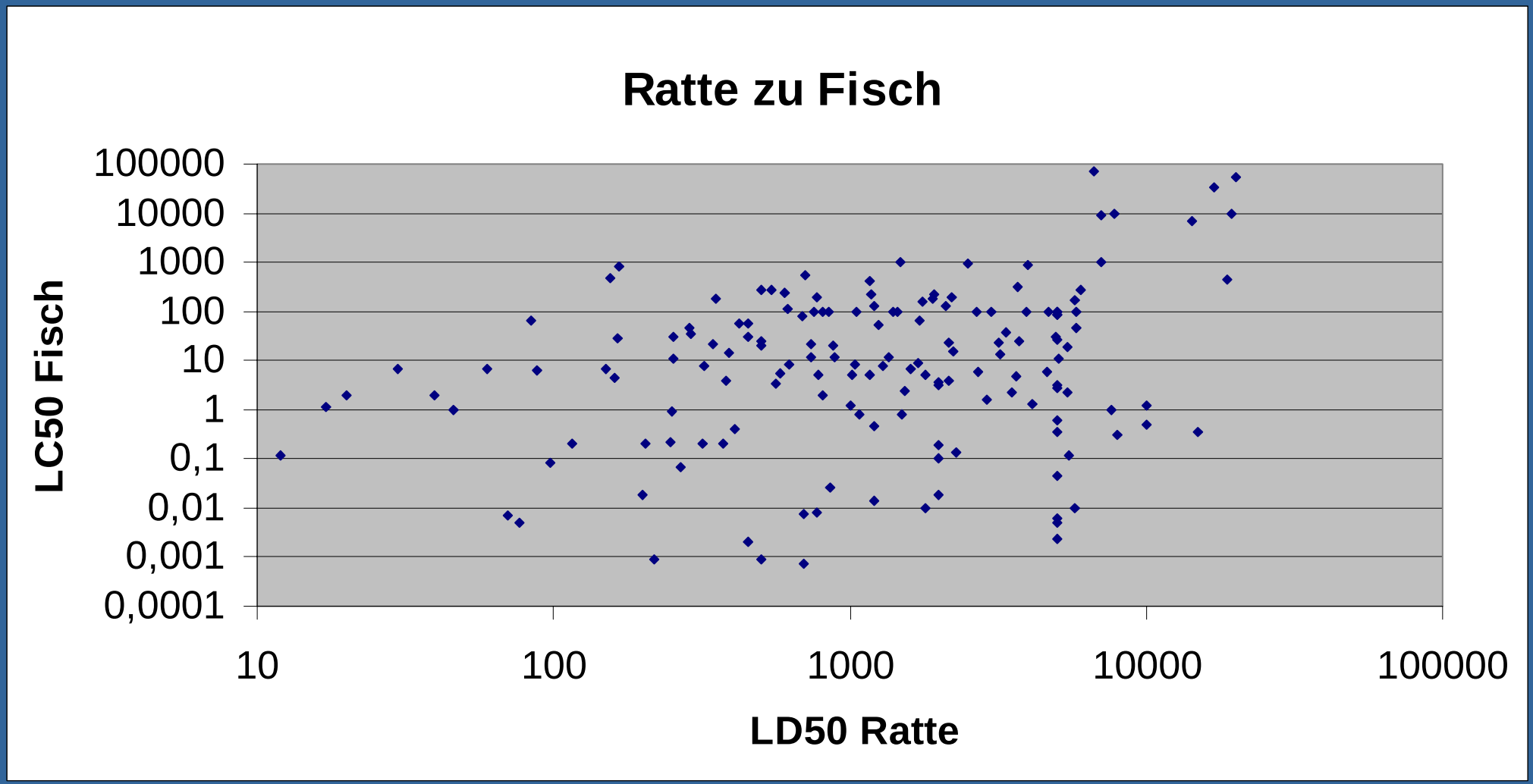
- To develop new in vitro methods that fit into the 3R-concept
- To establish in vitro methods as screening tools for toxicological testing during early substance development

- Detection of sexual hormone disrupting potential: yeast assay for estrogens (YES) / androgens (YAS)
- Dermal absorption in vitro (artificial skin models)
- Ecological tests to predict acute mammalian toxicity

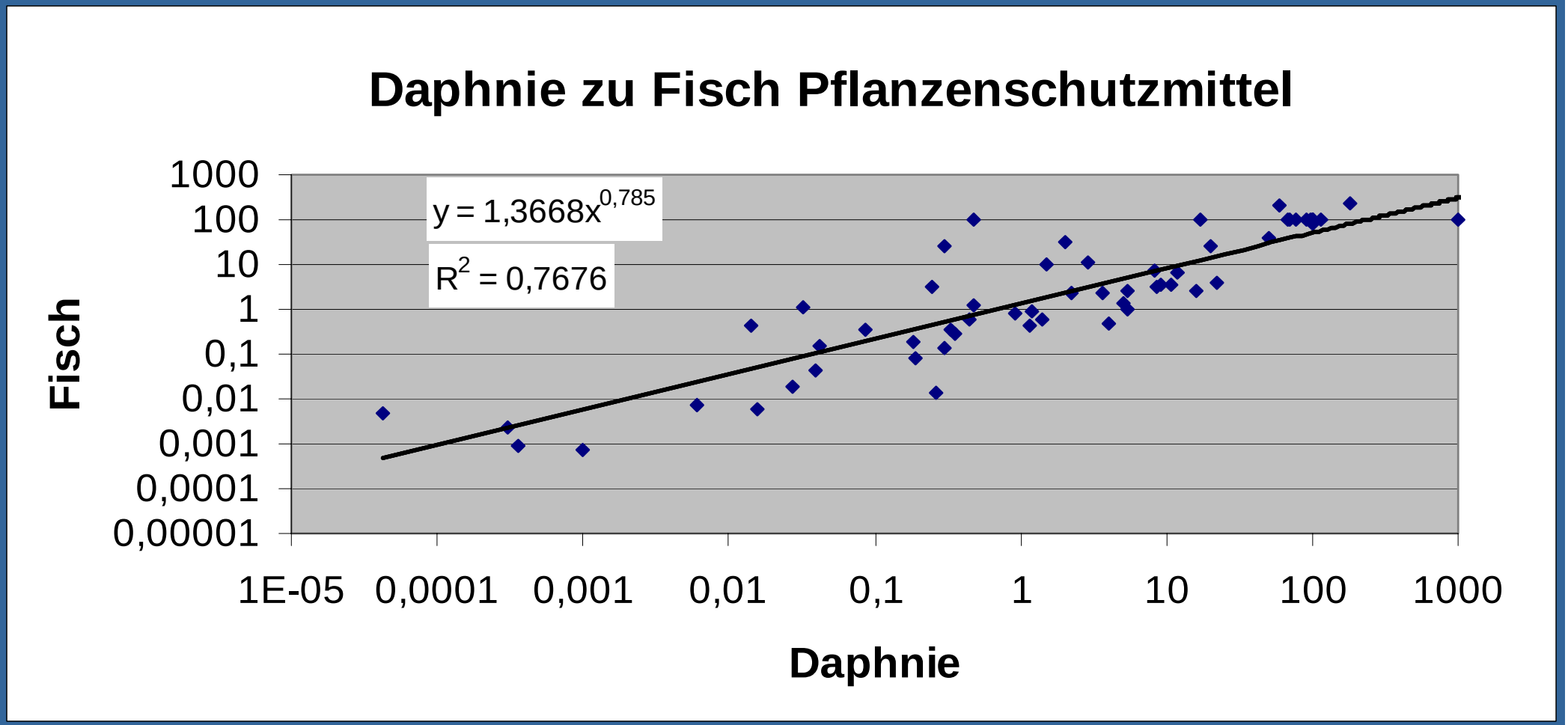
Ecological test for mammalian toxicity



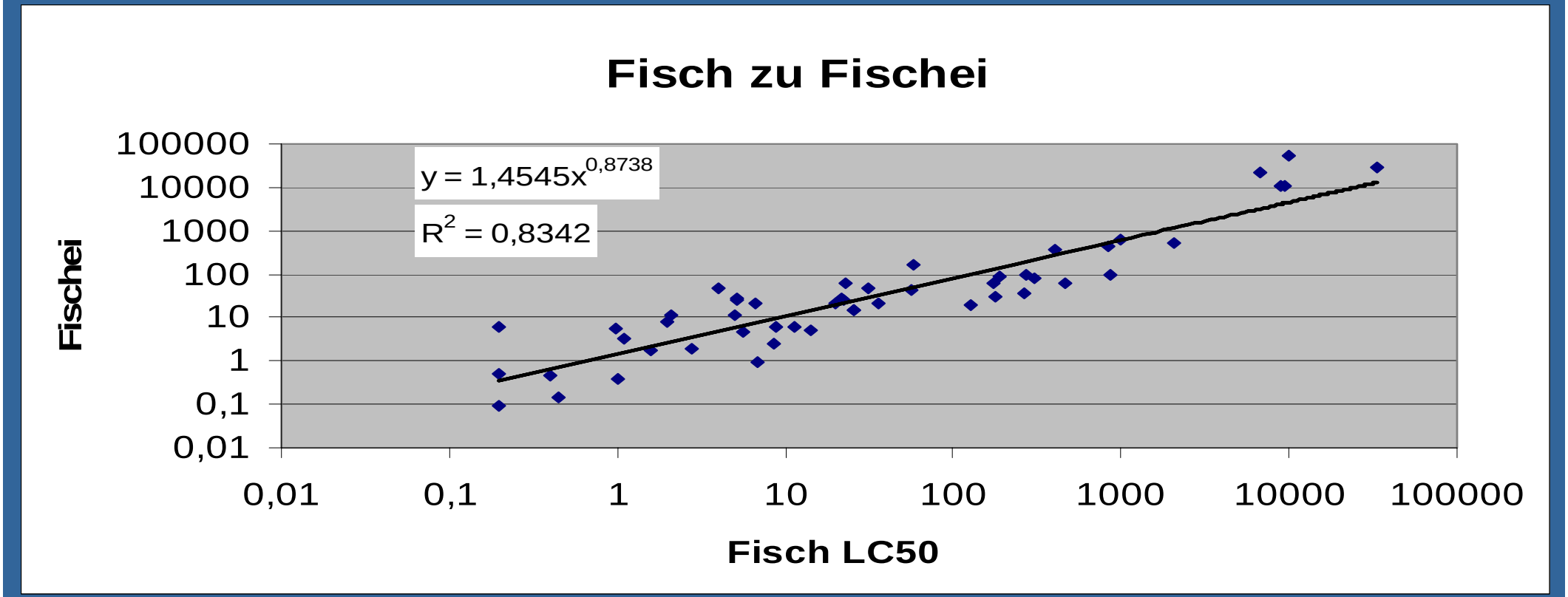
Ecological test for mammalian toxicity



Ecological test for mammalian toxicity



Ecological test for mammalian toxicity



Role of alternatives in REACH and Intelligent Testing ?

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Intelligent Testing “Toolbox”

- In vitro tests: Yes, but we have to manage expectations !

  SCCNFP review of in vitro replacements (2004)

Reproductive toxicity	>>2014 (not foreseeable)
Skin sensitisation	> 2019
Subchronic toxicity	>>2014 (not foreseeable)
Genotoxicity/mutagenicity	> 2016
ADME	>>2014 (not foreseeable)
Carcinogenicity	>>2014 (not foreseeable)

Role of alternatives in REACH and Intelligent Testing ?

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- Read-across:
  is case by case & needs to be justified

  Follow US HPV example
  from individual waiving / reduced data requirements
  to group-wise testing strategies

Role of alternatives in REACH and Intelligent Testing ?

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Intelligent Testing “Toolbox”

- Read-across – an example – from CCPA to MCPA

  Accordingly, for read across we propose the following information set:

  1) Information of acute toxicity (e.g. acute oral LD50),
  2) Information on genotoxicity (e.g. Ames test),
  3) Information on the most relevant end points for multiple exposure relative to the toxicological profile of the reference molecule, and,
  4) Expert judgement concerning the kinetics.

Reg Tox Pharm, 42, 47-54, 2005

Role of alternatives in REACH and Intelligent Testing ?

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Intelligent Testing “Toolbox”

- Optimised in vivo tests & test strategies

  LLNA
  Enhanced OECD 407 / 90 day rat + OECD 414

  Use of ‘omics in hazard identification:

  More information & possibility of predictive toxicology may be used to reduce number of animals in classical OECD guideline studies without loss of sensitivity and ability to assess toxic effects

Role of alternatives in REACH and Intelligent Testing ?

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Intelligent Testing “Toolbox”

- Tiered / Triggered Testing

  ILSI / HESI
  Agricultural Chemical Safety Assessment
  - Systemic Toxicity White Paper
    - 40% reduction of animals used for testing

http://www.ilsi.org/file/SystToxDraftPaperJan05.pdf

CONCLUSION

- To manage REACH: Use all possibilities that the "Intelligent Testing Toolbox" has to offer
  - Exposure-based waiving / testing
  - Threshold of toxicological concern
  - SARs and QSARs
  - In-vitro tests
  - Read-across
  - Optimised in-vivo tests
  - Tiered / Triggered testing
- Industry and Autorities have to be Pragmatic
- Focus on Risk Assessment
- Have the courage to think "out of the box"