# *Strategic Testing in REACH*
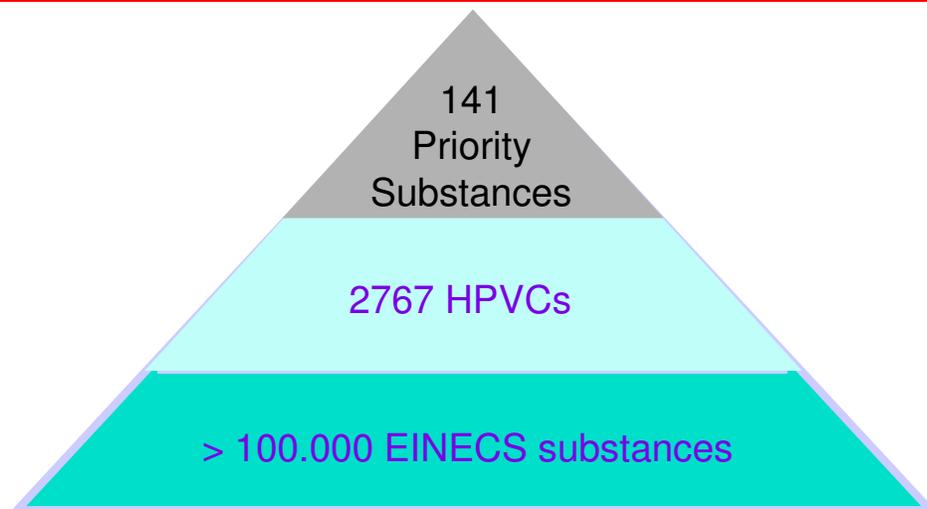# *A Testing Paradigm Shift*

**Kees van Leeuwen**

**TNO Quality of Life**
**Zeist, The Netherlands**

## CONTENTS

1. Introduction
2. Data requirements
3. REACH and the use of animals
4. Concluding remarks
5. International QSAR & ITS activities
6. Further REACH guidance and tools

## The data: current situation in EU

141
Priority
Substances

2767 HPVCs

> 100.000 EINECS substances

## Public Availability of Data on HPVCs
(Allanou, Hansen and van Der Bilt, 1999)

- 14 %:base set data

- 65%: less than base set

- 21%: no data

86%

## What is the aim of a CSA?

The CSA of a chemical substance aims to establish the safe conditions of manufacture and use of a substance for all life-cycle stages. Manufacturers, importers and downstream users of substances on their own or in preparations have to ensure that these are manufactured and can be used in such a way that human health and the environment are not adversely affected.

## 2. Data requirements

*Annex VII (≥ 1 tonne per year)*
- Physicochemical properties
- Human health: *in vitro* irritation, sensitization, mutagenicity, acute toxicity (one route)
- Environmental: acute aquatic toxicity (daphnia, algae), biodegradation

*Annex VIII (≥ 10 tonnes per year)*
- Human health: including *in vivo* irritation, and 28-day repeat dose studies
- Environmental: acute toxicity fish, fate studies (hydrolysis, adsorption / desorption)
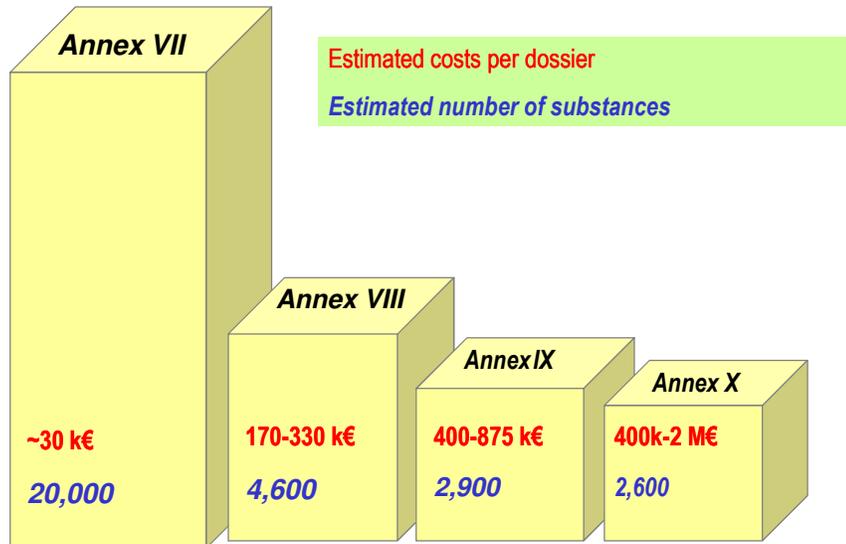
*Annex IX ( ≥ 100 tonnes per year)*
- Long term, repeat dose, chronic toxicity, fate etc

*Annex X (≥ 1000 tonnes per year)*
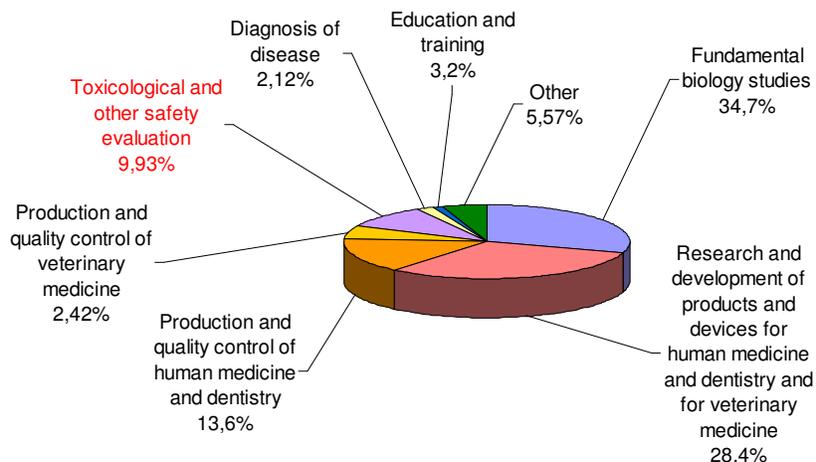- Further long term, repeat dose, chronic toxicity, fate etc

# REACH data requirements

Annex VII

Estimated costs per dossier

Estimated number of substances

Annex VIII

Annex IX

Annex X

~30 k€

170-330 k€

400-875 k€

400k-2 M€

20,000

4,600

2,900

2,600

---

## 3. REACH and the use of test animals

- Testing on vertebrate animals shall be undertaken only as a last resort (Art. 25)

- Information may be generated by other means than tests, in particular through *in vitro* methods, (Q)SARs and read-across (Art. 13)

$\Rightarrow$ Legislative text + guidance should limit use of animals and prevent box-ticking

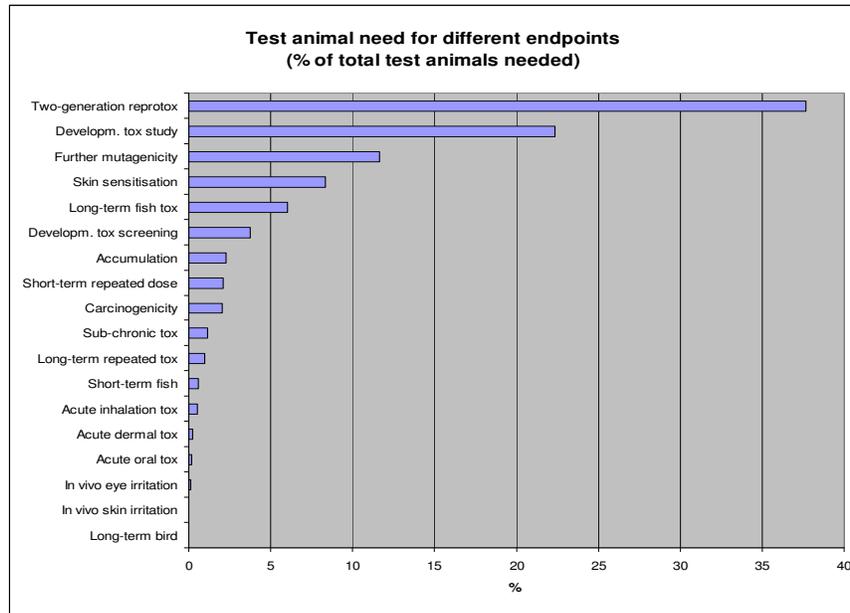**Use of animal experiments in the EU in 2002**
**COM(2005) 7 final**

Diagnosis of disease
2,12%

Education and training
3,2%

Toxicological and other safety evaluation
9,93%

Other
5,57%

Fundamental biology studies
34,7%

Production and quality control of veterinary medicine
2,42%

Production and quality control of human medicine and dentistry
13,6%

Research and development of products and devices for human medicine and dentistry and for veterinary medicine
28,4%

total number in 2002 = 10.7 million

---

**Purposes of animal experiments in 2002**
**COM(2005) 7 final**

| | | |
|---|---|---|
| Total number | 10,700,000 | 100 % |
| Safety evaluations | 1,060,000 | 10 % |
| Agricultural chemicals | 123, 000 | 1 % |
| Industrial chemicals | 136,000 | 1% |
| Cosmetics | 2,700 | 0.025% |

**Estimated test animal need (van der Jagt et al., 2004)**

**Test animal need for different endpoints**
**(% of total test animals needed)**

| Endpoint | % |
|---|---|
| Two-generation reprotox | ~37.5 |
| Developm. tox study | ~22 |
| Further mutagenicity | ~11.5 |
| Skin sensitisation | ~8 |
| Long-term fish tox | ~6 |
| Developm. tox screening | ~4 |
| Accumulation | ~2 |
| Short-term repeated dose | ~2 |
| Carcinogenicity | ~2 |
| Sub-chronic tox | ~1 |
| Long-term repeated tox | ~1 |
| Short-term fish | |
| Acute inhalation tox | |
| Acute dermal tox | |
| Acute oral tox | |
| In vivo eye irritation | |
| In vivo skin irritation | |
| Long-term bird | |

%

# Three tests determine the cost

Currently no alternatives to animal testing are available for the three main contributors to the overall test animal use and costs:

1. two-generation reprotoxicity
2. developmental toxicity studies
3. further mutagenicity (*in vivo*) study

These studies contribute with approximately 70% to the total test animal needs and testing costs.

## Cost-saving aspects:
## Intelligent Testing Strategies

The most efficient way to carry out hazard and risk assessments of large numbers of chemicals, while reducing costs to industry and minimising animal testing, is to obtain the necessary information by means of intelligent testing strategies (ITS).

Intelligent testing strategies are integrated approaches comprising of multiple elements aimed at speeding up the risk assessment process while reducing costs and animal tests

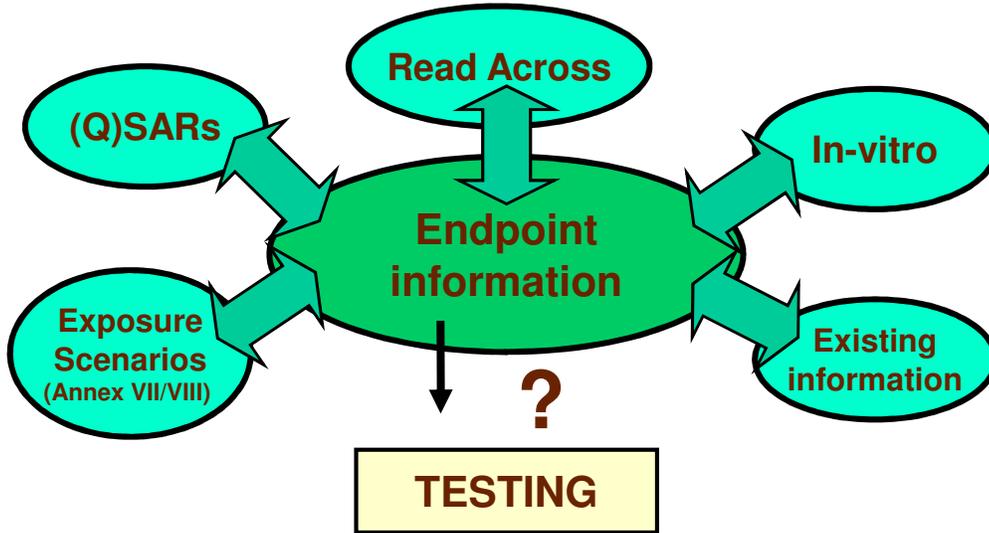(Bradbury, Feytel and Van Leeuwen, 2004)

---

# REACH: saving potential of ITS
### (Van der Jagt et al., 2004; EUR report 21405)

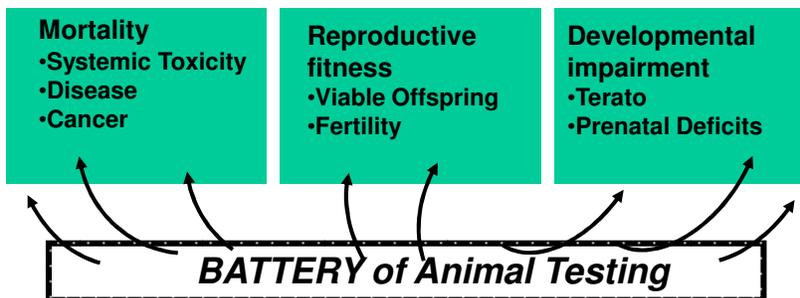⇨**Testing costs**:         **€ 800-1130 million**

⇨**Number of animals**:    **1.3-1.9  million**

**The most likely scenario for REACH according to the JRC: 2.6 million vertebrate animals and € 1.5 billion for testing (http://ecb.jrc.it/ )**

## Intelligent Testing Strategies (ITS)

**Read Across**

**(Q)SARs**

**In-vitro**

**Endpoint information**

**Exposure Scenarios**
**(Annex VII/VIII)**

**Existing information**

**?**

**TESTING**

---

Current toxicology testing paradigm generates *in vivo* animal data for all possible outcomes to determine which of all possible effects are relevant

**Mortality**
•Systemic Toxicity
•Disease
•Cancer

**Reproductive fitness**
•Viable Offspring
•Fertility

**Developmental impairment**
•Terato
•Prenatal Deficits

*BATTERY of Animal Testing*

(Jones and Bradbury,  USEPA, 2005)

## Components of Intelligent Testing Strategies
### (v) Read-across and chemical categories (USEPA, 2004)

|  | Human health | Environmental effects |
|---|---|---|
| **Adequate studies** | 50% | 58% |
| **Estimation via read-across** | 44% | 35% |
| **Testing** | **6%** | **7%** |

## A paradigm shift is needed

In the context of regulatory programs, the challenge is to move in a scientifically credible and transparent manner from a paradigm that requires extensive hazard testing to one in which a hypothesis- and risk-driven approach can be used to identify the most relevant *in vivo* information

(Bradbury, Feytel and Van Leeuwen, 2004)

# Towards a 7-R strategy implementing ITS

1. ***Risks*** Focus on risks (include **exposure**)
2. ***Repetitive*** A tiered approach should be applied, going from simple, to refined or comprehensive, if necessary, to quickly assess chemicals of low concern and to prevent animal testing.
3. ***Relatives*** The focus should be on families or categories of chemicals (a group-wise approach) using read-across, QSARs and exposure categories: move away from the chemical-by-chemical approach.
4. ***Restriction*** of testing (waiving of testing) where possible and carry out *in-vivo* testing where needed in order to prevent damage to human health and/or the environment. The strategy should also encompass the current 3-R strategy of:
5. ***Replacement*** (substitution)
6. ***Refinement*** (reduce suffering and distress)
7. ***Reduction***

# REACH, registration and ITS

- Increased pressure to use/develop alternative methods (Limited impact now but may influence future acceptance of methods)

- Agency in cooperation with MSs and interested parties should develop appropriate guidance (REACH Recital 38)

# 4. Concluding remarks

1.  Expectations to replace animal tests with *in vitro* studies and QSARs seem to be running ahead of scientific reality (see CSTEE & SCCNFP in Van Leeuwen, Patlewicz, Worth, 2007 and Greim et al. 2006)
2.  A paradigm shift is needed from extensive animal testing to efficient, focussed animal testing applying the 7-R approach
3.  ITS has a great animal-saving and cost-saving potential
4.  Guidance on data requirements (RIP 3.3) is available in draft form (see website of the ECB; 1100 pages!
5.  Further scientific work (2007 onwards) and regulatory implementation is needed.

# 5. International QSAR & ITS Activities

*   Category approaches (USEPA - Tala Henry)
*   Toxcast (USEPA- Focus on HTS)
*   Toxicity Testing in the Twenty-first Century (US NRC)
*   OECD QSAR Toolbox (Ovanes Mekenyan)
*   OECD Integrated Approaches to Testing and Assessment
*   EU Guidance document on data requirements (RIP 3.3 - European Chemicals Bureau)
*   OSIRIS (EU Project - Gerrit Schüürmann)
*   CAESAR (EU Project- Emílio Benfenati )

# 6. Further REACH guidance and tools

❑ Website of the European Chemicals Bureau:  http://ecb.jrc.it/reach/
❑ Website of the European Chemicals Agency:
   http://ec.europa.eu/echa/home_en.html
❑ Websites of the European Commission
   http://ec.europa.eu/environment/chemicals/reach/reach_intro.htm
   http://ec.europa.eu/enterprise/reach/index_en.htm
❑ http://ecb.jrc.it/DOCUMENTS/REACH/REACH_in_brief_0207.pdf
❑ Helpdesks of the EU member states, i.e.:
   http://www.reachright.ie
   http://www.senternovem.nl/reach

❑ Haigh N Baillie A. 1992. Final report on chemicals control in the European Community in the 1990s. Institute for European Environmental Policy, London, UK.

❑ Allanou R, Hansen BG, Van Der Bilt Y. 1999. Public availability of data on EU high production volume chemicals. Report EUR 18996 EN, European Commission, Joint Research Centre, Ispra, Italy.

❑ Van der Jagt K, Munn S, Tørsløv J, De Bruijn J. 2004. Alternative approaches can reduce the use of test animals under REACH. Addendum to the report "Assessment of additional testing needs under REACH. Effects of (Q)SARs, risk based testing and voluntary industry initiatives". Report EUR 21405. European Commission,Joint Research Centre, Ispra, Italy. Bradbury S, Feijtel T, Van Leeuwen K. 2004. Meeting the scientific needs of ecological risk assessment in a regulatory context. Environ Sci Technol 38/23, 463-470a.

❑ Scientific Committee on Cosmetic Products and Non-Food products intended for Consumers. 2004. The report for establishing the timetable for phasing out animal testing for the purpose of the cosmetics directive issued by ECVAM (30/4/2004). SCCNFP/0834/04. Brussels, Belgium.

❑ Jones, J. 2006. National Pesticide program. A new toxicological testing paradigm: meeting common needs. Presentation to the National Research Council Committee on toxicity testing and assessment of environmental agents on January 19. Irvine, CA. USEPA-OPP, Washington DC.

❑ Greim, H. et al. 2006. Toxicological comments to the discussion about REACH. Arch Toxicol 80:121-124

❑ Commission of the European Communities. 2007. Corrigendum to Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC (OJ L 396, 30.12.2006). OJ L136, volume 50, 29 May 2007.

❑ Guidance document on data requirements (RIP 3.2). See website ECB

❑ Van Leeuwen, C.J., G.Y. Patlewicz, and A.P. Worth. 2007. Intelligent Testing Strategies In: Risk Assessment of Chemicals. An Introduction (2nd edition). Van Leeuwen, C.J. and T.G. Vermeire, eds. Springer Publishers, Dordrecht, The Netherlands, pp 467-509.

❑ Van Leeuwen, C.J., B.G. Hansen and J.H.M. de Bruijn. 2007. Management of industrial chemicals in the European Union (REACH). 2007. In: Risk Assessment of Chemicals. An Introduction (2nd edition). Van Leeuwen, C.J. and T.G. Vermeire, eds. Springer Publishers, Dordrecht, The Netherlands, pp 511-551.

❑ National Research Council, 2007. Toxicity Testing in the Twenty-first Century: A Vision and a Strategy. The National Academic Press, Washington DC.
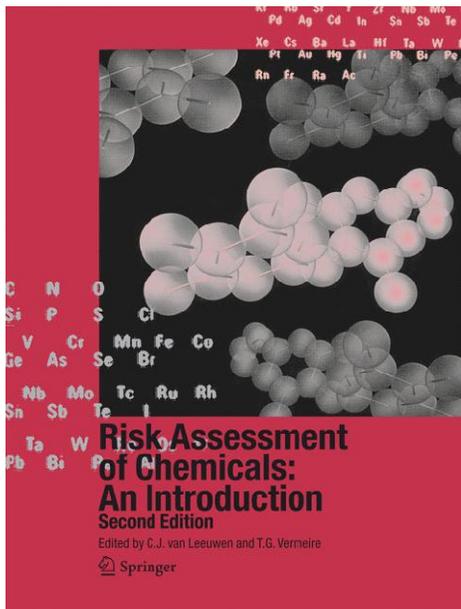
**Risk Assessment of Chemicals: An Introduction**

C.J. van Leeuwen and T.G. Vermeire (Eds.)

- **Written for:** Students in chemical technology, health and environmental sciences; risk assessors and managers worldwide; stakeholders involved in implementing REACH

- **Keywords:** chemicals, environment, health, reach risk

- 2007. 2nd ed. XXXII, 688 p. Hardcover

- ISBN: 978-1-4020-6101-1

## Data requirements under REACH  Annex VII for ≥ 1 TONNES

### Skin irritation or skin corrosion

| | |
|---|---|
| 8.2 | Eye irritation |
| 8.3 | Skin sensitisation |
| 8.4.1 | Mutagenicity (gene mutation in bacteria) |
| 8.5.1 | Acute toxicity (oral route) |

### Ecotoxicological information

| | |
|---|---|
| 9.1.1 | Short-term toxicity invertebrates (*Daphnia*) |
| 9.1.2 | Growth-inhibition plants (algae) |
| 9.2.1.1 | Ready biodegradability |

---

## Data requirements under REACH  Annex VIII for ≥ 10 TONNES

### Toxicological information

| | |
|---|---|
| 8.1.1 | Skin irritation (*in vivo*) |
| 8.2.1 | Eye irritation (*in vivo*) |
| 8.4.2 | Cytogenicity in mammalian cells (*in vitro*) |
| 8.4.3 | Gene mutation in mammalian cells (*in vitro*) |
| 8.5.2 | Acute toxicity (inhalation) |
| 8.5.3 | Acute toxicity (dermal) |
| 8.6.1 | Repeated dose toxicity (28days) |
| 8.7.1 | Reproductive/developmental toxicity screening test; OECD 421 or 422 |
| 8.8.1 | Toxicokinetics |

### Ecotoxicological information

| | |
|---|---|
| 9.1.3. | Short-term toxicity fish |
| 9.1.4. | Activated sludge respiration inhibition test |
| 9.2.2.1 | Hydrolysis as a function of pH |
| 9.3.1 | Adsorption/desorption screening test |

# Data requirements under REACH Annex IX for ≥ 100 TONNES

## Toxicological information

| | |
|---|---|
| 8.6.1 | Repeated dose toxicity (28 days) |
| 8.6.2 | Sub-chronic toxicity (90 days) |
| 8.7.2 | Developmental toxicity; OECD 414 |
| 8.7.3 | Two-generation reproductive toxicity study |

## Ecotoxicological information

| | |
|---|---|
| 9.1.5 | Long-term toxicity invertebrates (*Daphnia*) |
| 9.1.6. | Long-term toxicity to fish |
| 9.1.6.1 | Fish early-life stage test |
| 9.1.6.2 | Fish short term toxicity embryo and sac fry |
| 9.1.6.3 | Fish juvenile growth test |
| 9.2.1.2 | Ultimate degradation in surface water |
| 9.2.1.3 | Soil simulation testing |
| 9.2.1.4 | Sediment simulation testing |
| 9.2.3 | Identification of degradation products |
| 9.3.2 | Bioaccumulation in aquatic species (fish) |
| 9.3.3 | Further information on adsorption/desorption |
| 9.4.1 | Short-term terrestrial toxicity (invertebrates) |
| 9.4.2 | Effects on soil micro-organisms |
| 9.4.3 | Short-term toxicity to terrestrial plants |

# Data requirements under REACH Annex X for ≥ 1000 TONNES

## Toxicological information

| | |
|---|---|
| 8.6.3 | Long-term repeated toxicity (≥12 months) |
| 8.7.2 | Developmental toxicity; OECD 414 |
| 8.7.3 | Two-generation reproductive toxicity |
| 8.9.1 | Carcinogenicity study |

## Ecotoxicological information

| | |
|---|---|
| 9.3.4 | Further fate and behaviour in the environment of the substance and/or degradation products |
| 9.4.4 | Long-term toxicity on invertebrates |
| 9.4.6 | Long-term toxicity on plants |
| 9.5.1 | Long-term toxicity to sediment organisms |
| 9.6.1 | long-term toxicity to birds |