Waiving von Datenanforderungen und Optionen zum

Daten-Waiving bei Bioziden

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Gegenbeispiele aus der Praxis

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Overview of Presentation

- **Introduction: Data requirements for biocidal active substances, biocidal products and substances of concern**
- **Justification for the non-submission of data: Guidance on Data Waiving**
- **Concept for Data Waiving: Data collection – Read across/Bridging-Worst case exposure/risk assessments**
- **ITS: Intelligent/Integrated Testing Strategies and Establishment of "Points of Reference"**
- **Summary**

Data requirements for biocidal active substances, biocidal products and substances of concern

- **BPD/BPR: D**ifferentiation between common Core Data Set (CDS) and Additional Data Set (ADS)
  - ADS depending on the characteristics of the active substances, the product type and on the expected exposure of humans, animals and the environment in the intended use(s).

- **Ideal situation:**
  - Guideline and GLP compliant study data are submitted for each endpoint which is in compliance with Technical Notes for Guidance on data requirements: "*All data specified in a common core data set must be addressed in accordance with detailed guidance given in the TNsG*".
  - "Ideal" situation: Given in the authorization of PPPs for instance where no (or only a few) data gaps are identified.

Data requirements for biocidal active substances, biocidal products and substances of concern

Reality for biocidal active substances:

- For many/most biocidal active substances, only a limited data set is available (full data set rather an exception).
- Extent of availability of data e.g. human health (in decreasing order):

  Acute toxicity/primary irritancy/skin sensitisation.

  Subacute toxicity, mutagenicity.

  Higher tier endpoints such as CMR properties.

  (very often not available or information is limited, not guideline compliant and/or not fully valid)

Data requirements for biocidal active substances, biocidal products and substances of concern

- **Current practice to address data requirements for biocidal active substances:**

  - Data gaps are either not or only in rare cases closed by study data on the active substance (especially for higher tier studies).
  - Where available and feasible, alternative (= structurally related) substances are used.
  - Submission of data is not considered to be required → **"Justification for Non-Submission of Data = DATA WAIVER!"**.
  - Waiver: Scientifically sound and robust argumentation to be established!

Data requirements for biocidal active substances, biocidal products and substances of concern

Biocidal products:

- **In most cases:** Study data on the formulation are not available → properties of biocidal products addressed by waivers which is a valid procedure because

  a) data requirements for BPs less comprehensive/ less complex than those for the a.s.

  b) potential health/environmental effects (except data on PC properties) can be derived on the basis of information available for individual components **or** product data are not meaningful (e.g. ready biodegradability of product).

  c) bridging principles for similar (tested) formulation can be applied.

  d) MSDS information on (co)formulants may be considered (**NB:** Validity/Robustness to be confirmed!).

- **Important:** Necessity of generation of product data dependent on the characteristics of components in the biocidal product; consideration of similar/dissimilar modes of action of the ingredients and their targets; conclusion on synergistic or additive effects!

Data requirements for biocidal active substances, biocidal products and substances of concern

Substances of Concern (SoC):

- **SoC: Substances other than the active substance** present in the b.p. which due to their classification or (eco)toxicological properties give rise to a potential (health) concern.
- Study data (especially risk assessment relevant endpoints) on these substances is very often scarce and a REACh registration dossier is **not** or **not yet** available.
- **Potential SoCs will receive more attention** in the evaluation of biocidal products in the future.
- SoC guidance is presently under development.
- **Objective:** Ensure a high level of protection for humans, animals and the environment whilst applying a pragmatic approach in parallel. Knowledge on SoC needed for the purpose of exposure and risk assessments.

Justification for Non-Submission of Data – Guidance on Data Waiving

- **Waiving concept based on TNsG on Data Requirements and the General Rules for the Adaptation of the Data Requirements (Annex IV of BPR):**

  - **Basic principle:** All data specified in a common core data set must be addressed in accordance with the TNsG on Data Requirements. Common core data is a minimum set required for all substances and product types.

  - Important: **Only in exceptional circumstances** studies comprising the core data set, i.e. up to and including the 28/90 day repeat dose studies in the rat, and the ADME package can be waived.

Justification for Non-Submission of Data – Guidance on Data Waiving

- **Waiving of data requirements of the common core data set (i.e. section points 6.1 through 6.8 + 6.12 for human health in the BPD or section points 8.1 through 8.12 in the BPR) may be possible case by case based on**

  - Considerations on the technical feasibility and the scientific necessity of a study in view of the intended uses: Volatile substances → testing only via the inhalation route = primary route of exposure; Effects of corrosive substances are predictable → primary local effects.

  - Considerations on the availability of alternative or other existing data: Read across/bridging; Waiving of second (non-rodent) species study in case of experience from veterinary medicinal use.

Justification for Non-Submission of Data – Guidance on Data Waiving

- **Waiving of data requirements of the common core data set (cont'd)**

  - Toxicological considerations following assessment of available (adequate) data including human experience during the intended use(s) and identification of options for waiving of further studies.

  - Consideration of human exposure/general profile of exposure to the product in combination with the toxicity profile of the individual active substance(s): need for extensive toxicological testing should take into account primary and secondary exposure with regard to level, frequency and duration of exposure.

Justification for Non-Submission of Data – Guidance on Data Waiving

- **Justified waiving of e.g. animal studies** (and compliance with 3R principle) if:

  - **Low/negligible exposure** is confirmed: Level of exposure at or below the threshold for lower concern (for instance: MOS > 1000; frequency and duration of exposure is low).
  - **A valid in vitro method** is available; NB: presently only validated and accepted for local effects on the skin/eyes and genotoxicity.
  - **Validated QSARs** provide required information and QSAR is applicable to substance.
  - **Weight of the evidence of all available information** including data on structural analogues allows for an adequate assessment of the endpoint of concern.

Justification for Non-Submission of Data – Guidance on Data Waiving

- **Further justification on waiving of e.g. animal studies based on experience gained in the evaluation process:**

"A (vertebrate) study of the common core data set should not be performed for reasons of animal welfare when it does not provide further essential information on the substance characteristics":

- **Mode of action and/or target** is known and not expected to differ across species: Effects are predictable in a second (non-rodent) species.
- **Results from available subacute/subchronic studies** including dose-range-finders **provide no evidence for a dependence of substance-related effects on study/exposure duration** and no chronic/long-term studies are needed.
- Results from a **well-conducted and extended subchronic (90-day) study in combination with a teratology study** indicate no effects on reproductive organs and accessory glands: Waiving of the 2-generation reproductive toxicity study.

Concept for Data Waiving

Generation of a basic data set in order to

- Identify the critical effects resulting from exposure to the substance**.**
- Identify the mode of action and targets: Knowledge on the mode of action important for building of waiving arguments (proven local mode of action and non-systemic availability reduce data requirements and comply with animal welfare).
- Enable the preparation of robust waivers for other non-tested endpoints of the core data set and to decide on the need/absence for a need of additional data depending on the intended uses*.

***Note:**

Waiving arguments are built on available information considering in parallel a weight-of-the-evidence approach → some data are indispensable otherwise there is no solid basis for waiver building.

Concept for Data Waiving

Data collection – Read-across/bridging

- Collect all information available on the active substance including human volunteer data, case reports, epidemiological studies and assess the validity/robustness of this information.

- Establish information on the mode of action of the active substance and on the active principle with emphasis on local and/or systemic effects.

- Where there are data gaps, collect available data on structurally related substances (same chemical class and functional groups) for the purpose of a read-across/bridging and confirm the applicability of these data (“category/grouping approach”).

Concept for Data Waiving

How to do read-across?

- Comparison of the results of endpoints available for the active substance and the structural analogue confirm or refute applicability of this approach.

- Comparison on structural grounds and considering parameters such as water solubility and $\log_{Pow}$ are basic criteria for applying a read-across.

Concept for Data Waiving

Establishing a “Point of Reference”

- When no or only very limited data are available:

a) Search for data on appropriate structural analogues

b) Create a “point of reference” (performance of selected studies) in order to prove the applicability of a read-across using data of structurally related substances.

Concept for Data Waiving

Worst case exposure/risk assessments

- Perform exposure/risk assessment for the intended uses assuming (realistic) worst case scenarios: maximum application rates/application frequency and application duration

→ Exposure based waiving possible if identified exposure scenarios are at or below the threshold of lower concern as provided for in TNsG on Data Requirements

Important:
Availability of dermal penetration to significantly reduce exposure via the dermal route → dermal route in many cases the exposure trigger!

Concept for Data Waiving

Application of the TTC Concept (= Threshold of Toxicological Concern)

- Further option with a view to data waiving.
- If there is a lack of toxicity data and active substance is not a high potency genotoxic substance: Investigate the application of the TTC concept and the “applicability domain” of Cramer classes I-III.
- Some knowledge on the substance needs to be available, otherwise a grouping into the appropriate Cramer class is hampered.

- TTC concept could be used as a screening level assessment.
- If exposure is estimated to be below the respective TTC threshold(s), waiving of study data may be acceptable.

- **Recommendation:** Discuss the TTC-concept strategy with the RMS prior to dossier submission and ensure availability of fadequate/sufficient exposure information.

Concept for Data Waiving

Application of the TTC Concept (cont'd)

- The TTC concept is applicable to substances grouped in Cramer classes I-III for each of which a general (tolerable) intake threshold is defined:

Group/category	TTC value [µg/person/day]
Substances with structural alerts for carcinogenicity/mutagenicity (analysis of 730 substances)	0.15
Substances without structural alerts for carcinogenicity/mutagenicity	1.5
Organophosphates (analysis of 19 substances)	18
Cramer class III: Substances with significant toxicity and reactive functional groups (analysis of 448 substances)	90
Cramer class II: Moderately toxic substances (analysis of 28 substances)	540
Cramer class I: Simple chemical structures with low order of oral toxicity (analysis of 137 substances)	1800

ITS: Intelligent/Integrated Testing Strategies – Experience from Practice

Substance with a lack of systemic (bio)availability

- **Highly reactive substance** are rapidly degraded at the site of first contact: Properties/effects are characterized by a local mode of action and a lack of systemic availability.

- **Evidence on the lack of systemic availability** to be provided from:

  a) Results of repeated dose toxicity studies (local effects only?) in combination with

  b) In vitro studies demonstrating rapid (enzymatic) degradation as supporting evidence.

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Substance with a lack of systemic (bio)availability (cont'd)

- If absence of systemic availability is confirmed: Only local exposure assessment and risk characterization for local effects required (Consideration of degradation products in systemic risk assessment!).

Note:

Basic data set consisting of acute toxicity/primary irritation/sensitisation studies including information on genotoxicity and repeated dose toxicity recommended in order to be able to prepare scientifically robust waivers and to substantiate lack of systemic availability.

ITS: Intelligent/Integrated Testing Strategies – Experience from Practice

Substance with systemic (bio)availability: Test strategy and waiving – example for an essential oil

- According to BPD/BPR: All data of the core data set would need to be generated as a minimum data set.
- **Assumption:** Except acute toxicity data package and irritation data, no higher tier toxicity data available (no repeated dose toxicity/CMR data) + due to special application, exposure assessment not possible (no suitable model available). Available data from the literature old and/or results do not allow for drawing firm conclusions on tox profile → **Data gaps identified.**
- Considerations on intended use(s): Primary exposure path identified to be the inhalation route.
- Decision for dossier strategy: Testing of primary exposure route (inhalation route) only.

ITS: Intelligent/Integrated Testing Strategies – Experience from Practice

- **Genotoxicity test battery conducted**

  In vitro bacterial mutation test: **positive**

  In vivo MNT in mice: **negative**

  In vivo UDS rat: **negative**

  Overall result: Active substance is not genotoxic

- **Repeated dose toxicity testing strategy and considerations on animal welfare**

  Performance of OECD 414 compliant teratology study in the rat (including dose range finder).

  Performance of subchronic inhalation study (including 14-day dose range finder) acc. to OECD 413 + recovery period + detailed investigations of reproductive organs and accessory glands.

ITS: Intelligent/Integrated Testing Strategies – Experience from Practice

- **Extension of study subchronic inhalation study:**

  Due to an “alert” from other available information, inclusion of neurotoxicity examinations (FOB/MA and neuropathology) according to OECD 424 → no separate subchronic neurotoxicity study needed!

  Examination of sperm parameters and oestrus cyclicity according to OECD 416.

- **Conclusion:** Testing programme on a “naïve” substance with no data allowed assessment of:

  Genotoxicity (= trigger for further dossier strategy).

  Subchronic (neuro)toxicity, teratology and reproductive performance.

  Potential neoplastic effects.

Establishment of “Points of Reference” – Experience from Practice

Read across and point(s) of reference

- **Assumption:** Four similar active substances (= natural inorganic substances), intended use(s) are identical.
- No data available for all active substances on “higher tier endpoints” (e.g. repeated dose toxicity and CMR properties) and data on acute toxicity and genotoxicity is limited.
- **Strategy:** Application of a read-across/bridging approach using available data from one of the active substances which possesses a valid and acceptable data set.
- In order to prove acceptability and robustness of a read-across to higher tier endpoint and to demonstrate a similar (toxicity) profile of all four active substances, **“points of reference”** have to be established.

Establishment of "Points of Reference" – Experience from Practice

Read across and point(s) of reference (cont'd)

- **Decision:** Testing of acute oral and acute dermal toxicity and performance of in vitro bacterial mutation tests.
- **Result:** All four substances provided very similar results in the tests conducted → Read-across approach feasible (and also accepted by RMS).

- **Conclusion:** Some **points of reference** need to be established for a read-across. Considerations on structural analogy and physical-chemical parameters serve as a first screening tool for the (pre)-selection of suitable read-across candidates.

Summary on Data Waiving (1)

- **Best case:**

  All data requirements can be fulfilled by valid study data.

- **Real case:**

  Not all data requirements are (in many cases) fulfilled by valid study data.

Summary on Data Waiving (2)

Recommended procedure:

- Collect all information available (study data, literature information, human health records).
- Identify data gaps.
- Undertake assessment of mode of action (local/systemic) and chemical behaviour/reactivity of active substance and conclude on necessity of further data taking into account nature of substance and exposure pattern.
- Investigate feasibility of a read across to structurally related substances ("category/grouping approach").
- If read across is possible: Comparison of data available for the active substance and the other substance(s) **or** create point(s) of reference to confirm the scientific robustness and validity of a read-across.
- If no data are available or a read-across is not possible or possible to a limited extent: Set up an intelligent testing strategy!

REFERENCES:

- Directive 98/8/EC ("BPD") of the European Parliament and of the Council concerning the placing of biocidal products on the market (OJ L123, 24 April 1998).

- Regulation (EC) No. 528/2012 of the European Parliament and of the Council of 22 May 2012 concerning the making available on the market and use of biocidal products (OJ L167, 27 June 2012).

- Technical Guidance Document in Support of the Directive 98/8/EC Concerning the Placing of Biocidal Products on the Market – Guidance on Data Requirements for Active Substances and Biocidal Products.

Thank you very much for your attention!