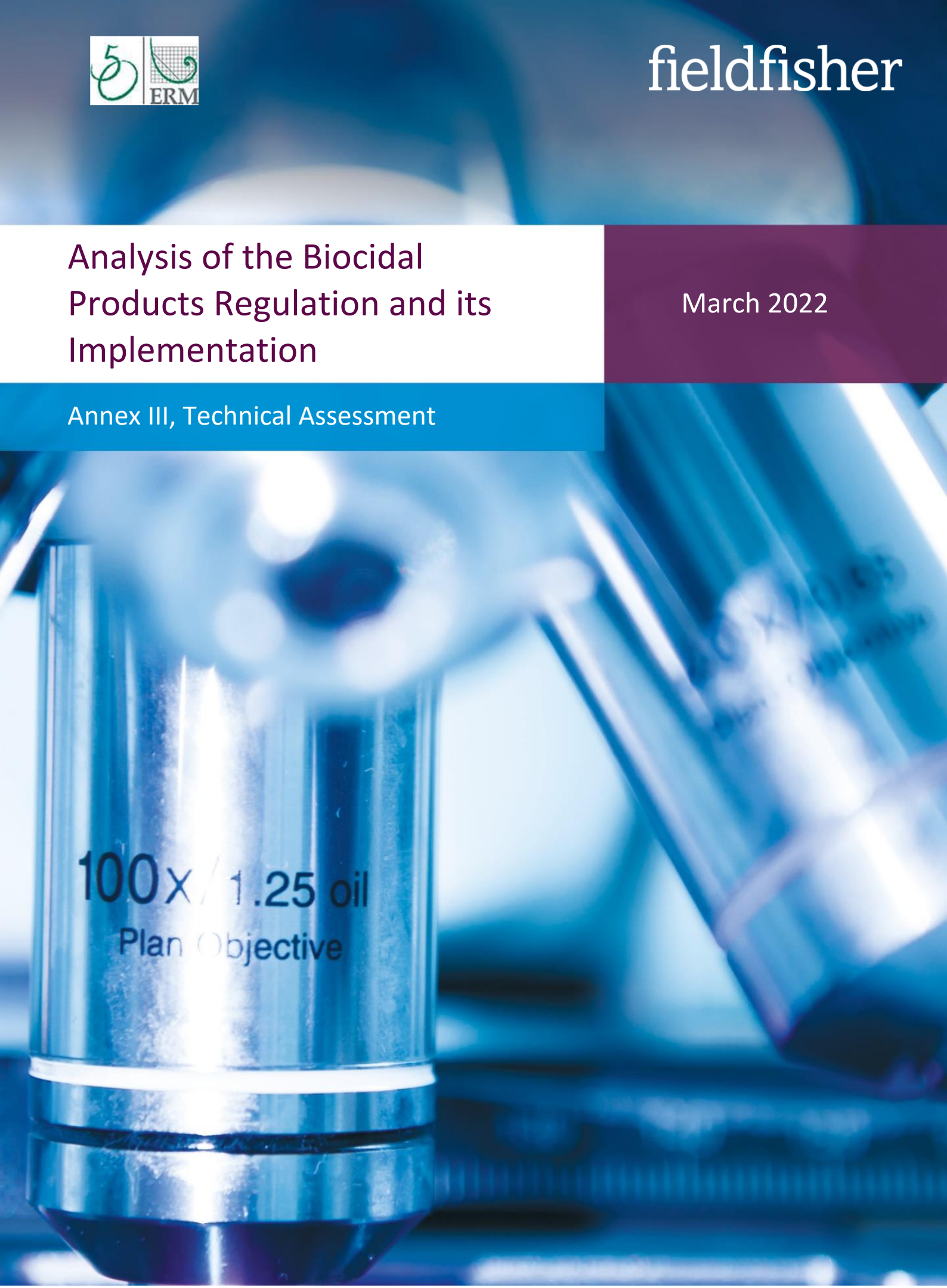
Analysis of the Biocidal Products Regulation and its Implementation

March 2022

Annex III, Technical Assessment



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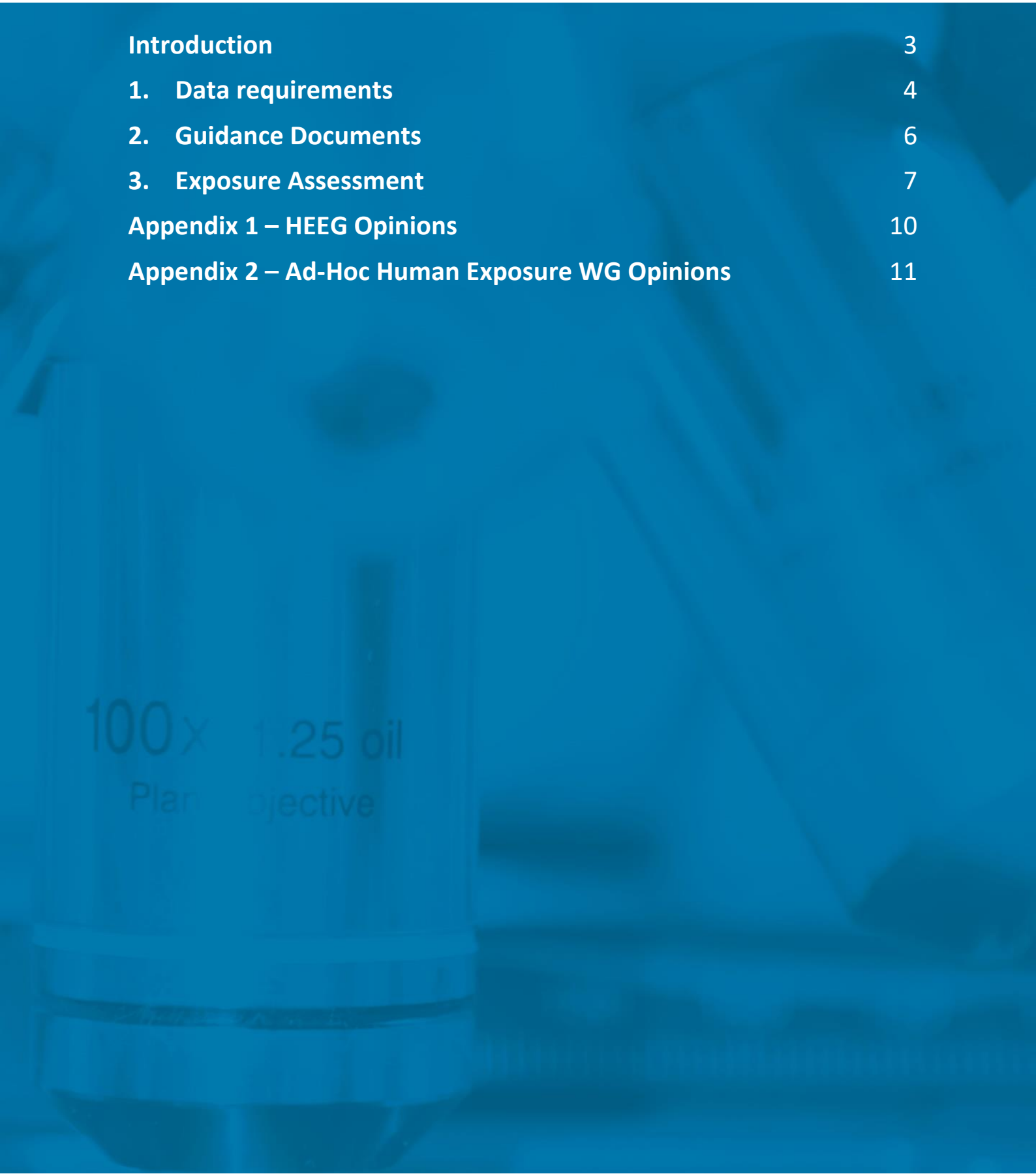


Introduction

The Biocidal Products Regulation (BPR) came into effect on 1 September 2013, establishing a new framework regulating the placing on the EU market of biocidal products and treated-articles. Biocides are used to control organisms that can, directly or indirectly, be harmful to human and animal health or cause material damage and include, for example, disinfectant, preservative and pest control products that act against these harmful organisms.

The BPR is a highly complex piece of chemical legislation that brings into its scope a huge variety of biocidal products and their uses, and the multitude of chemistries that these products contain. The technical evaluation required by the BPR to establish safe use of biocidal products must accommodate active substances with widely differing hazard profiles and products with a wide diversity of exposure potential for humans and the environment. At the same time, the technical evaluation must maintain a consistent, transparent and non-discriminatory treatment of each application. This represents a significant challenge.

A further challenge is reconciling the objective of the BPR to "e*nsure a high level of protection of both human and animal health and the environment*"; within a technical evaluation that balances the societal need for biocides against the intrinsic hazard they may pose, in a proportionate manner.

This Technical Assessment considers changes to the data requirements applicable under the BPR, the scope of the guidance available to applicants and evaluators and the methodology used to estimate exposure when evaluating the approval of active substances and authorisation of product under the Regulation.

1. Data requirements

The information required to support the approval of an active substance is listed in Annex II of the BPR, with the corresponding data requirements for biocidal products listed in Annex III. In general, the requirements are clear and in most cases are based on OECD type studies or similar recognised testing protocols that are familiar to Industry and Authority technical experts.

A 'complete' dossier is required to support applications for active substance approval and product authorisation (both under BPR and formally under the BPD), which is a dossier containing sufficient information (study data or other relevant sources) for the evaluating Authority to conduct its review.

As envisaged in the BPR, the need for study data can be adapted (waived) as outlined in Annex IV i.e. not submitting data on the grounds that i) testing does not appear scientifically necessary, ii) testing is not technically possible or iii) not required based on exposure considerations. However, the suitability of data waiving is often subjective and divergence of opinion is a source of uncertainty. Nevertheless, if applied in a pragmatic manner, data waiving is important to reduce reliance on test data particularly for non-critical data points and should be the first option considered where the BPR requires animal tests.

The Annex II and Annex III information requirements have recently been revised[1]. Notable changes include; tiered testing for properties such as irritation, neurotoxicity and genotoxicity that favour *in vitro* tests over *in vivo* tests, changing requirements for genotoxicity (replacing the UDS assay with an appropriate in vivo somatic cell genotoxicity assay) and accepting the extended one-generation reproductive toxicity study (EOGRTS) as a suitable test for long term reproductive effects. These changes are welcome, in particular the move to reduce the reliance on certain vertebrate animal tests and changes taking account of scientific advances since the BPR was written.

The changes to data requirements shown above followed discussion between the various biocide Stakeholders as envisaged in Article 85 of the BPR, which allows provisions of the Regulation to be adapted to scientific and technical progress, through delegated acts. The changes to Annex II and Annex III apply from 15 April 2022 but may be applied by Applicants from 15 April 2021, by way of derogation. The Regulation amending the BPR and implementing these changes is clear that applications for approval of actives and applications for authorisation of product submitted before 15 April 2022 shall be evaluated based on information requirements applicable on the day of submission of such applications. This is welcome as it avoids retrospective application of these changes, which is a problem that has caused uncertainty and delay in the function of the BPR on many occasions according to companies responding to the Survey.

Having clear data requirements is important to the smooth operation of the BPR, but equally important is the understanding of how the data will be interpreted. This type of information is made available through less 'legal' routes in guidance and opinions developed in an ongoing manner, for example in Working Groups. This 'learning by doing' approach has resulted in significant uncertainty especially where guidance and opinions are only available many years after the submission of dossier and often come from individual substance evaluations that as a result lack transparency.

Endocrine Disruptors

A key data requirement introduced by the BPR is the need to establish endocrine disruption (ED) criteria for active substances, but it was not until September 2017 – 4 years after the introduction of the BPR - that these criteria were finally clarified[2], with accompanying ECHA/EFSA guidance only available the following year in June 2018. The topic of ED is highly complex, with the main guidance document running to 135 pages. An ED Expert Group was established in February 2014, coordinated and hosted by ECHA to give advice to EU Member State competent authorities (under REACH and BPR) and ECHA.

[1] COMMISSION DELEGATED REGULATION (EU) 2021/525 of 19 October 2020 amending Annexes II and III to Regulation (EU) No 528/2012 of the European Parliament and of the Council concerning the making available on the market and use of biocidal products

[2] COMMISSION DELEGATED REGULATION (EU) 2017/2100 of 4 September 2017 setting out scientific criteria for the determination of endocrine-disrupting properties pursuant to Regulation (EU) No 528/2012 of the European Parliament and Council

The focus of attention on ED requires new studies that were not envisaged when review programme dossiers were submitted and are not part of the Annex II or Annex III data set. These tests are of a type not usually required in regulatory submissions (e.g. E-modality: uterotrophic bioassay (OECD 440), A-modality: Hershberger bioassay (OECD 441), S-modality: H295R steroidogenesis assay (OECD 456))[3]. Other non-standard studies required for ED assessment have only recently been included in the OECD suite of tests (e.g. XETA assay (OECD 248))[4]. These studies require further animal testing and test facilities capable of conducting the work with sufficient resource and expertise to interpret the results in a Regulatory context can be limited.

The impact of this additional data requirement on the review of active substances is significant to the point of delaying completion of the review beyond the stated end date of 31 December 2024. Of greater concern is the narrow focus on determining hazard criteria even to the point of investigating substances that are essential to endocrine function (e.g. iodine).

The need for additional testing should also consider the likelihood of exposure (risk) in a more balanced approach and there is a clear need to establish thresholds to trigger when effects need to be investigated. This is especially relevant in the case of impurities in active substances, where the presence of an impurity identified as an ED means the active substance itself is considered to have ED properties, unless demonstrated otherwise[5].

The investigation of ED effects is not restricted to active substances but has been further extended, with the need to consider the ED potential of non-active substance used as product co-formulants, with implications extending into other legislation (REACH). This retrospective change to the BPR data requirements has the potential to introduce further delay, cost and new testing requests into the review of biocidal products.

Other significant examples of retrospective changes to data requirements include nanomaterials, treated article efficacy, efficacy of co-formulants and disinfection by-products.

Nanomaterials

In the case of nanomaterials, the change required the reappraisal of active substance identity for substances already supported with dossiers submitted under the BPD and the provision of new data by Applicants to confirm substances did not meet new criteria defining nanomaterials.

Substances identified as nanomaterial attract special attention under the BPR and products require labelling to alert users to the (hazardous) presence of a nano material irrespective of the risk of exposure. An interesting example here is silicon dioxide used as an insecticide (PT18).

Synthetic amorphous silicon dioxide is a biocide active substance identified as a nanomaterial based on primary particle size and specific surface area by volume according to the Commission recommendation on the definition of nanomaterial (2011/696/EU). Available data showed that primary particles are aggregated (> 100 nm) and under conditions of normal use, it was considered that these aggregates are the smallest stable particles. In this context, liberation of primary particles and exposure to nano-objects was not expected and the hazard and risk of nano-particles of silicon dioxide was not evaluated (not required).

This highlights the potential for contradictory information to be communicated to users and the need for risk assessment to be at the forefront of regulatory decisions. Hazard should only be communicated to the user where it exists, otherwise the communication is misleading.

Efficacy

Efficacy requirements for treated articles have undergone fundamental changes under the BPR, with the ongoing development of guidance running parallel to review programme evaluations. These changes were influenced by Member State initiatives, for example the funding of a Working Paper on the Efficacy Assessment of Treated Articles[6] by the Nordic Council that informed a large part of the treated article update to the Guidance on the BPR: Volume II Efficacy, Assessment + Evaluation (Parts B+C) in February 2017.

[3] E, A and S refer to the so called EATS endocrine modalities (estrogenic, androgenic, thyroid and steroidogenic)
[4] Xenopus Eleutheroembryonic Thyroid Assay
[5] CA-March21-Doc.5.1- ED properties impurities.docx
[6] Efficacy Assessment of Treated Articles - A guidance http://dx.doi.org/10.6027/NA2014-904, NA2014:904, ISSN 2311-0562.

The changes require detailed information on the efficacy of articles in addition to demonstrations of the benefit of treating such articles, new information that moves the assessment of efficacy beyond a simple proof of innate efficacy that was the need previously for active substance approval. In addition, the claims made for treated articles have become the focus, with efficacy data needing to support exactly the claim made even for active substance approval where such data is not required[7].

A co-formulant being a potential active substance in a disinfectant product has also developed as an important topic since the introduction of the BPR, requiring a justification of its function in the formulation and how this influences the efficacy of the product. In cases where justification is not conclusive tests are required to demonstrate the 'non-activity' of the co-formulant.

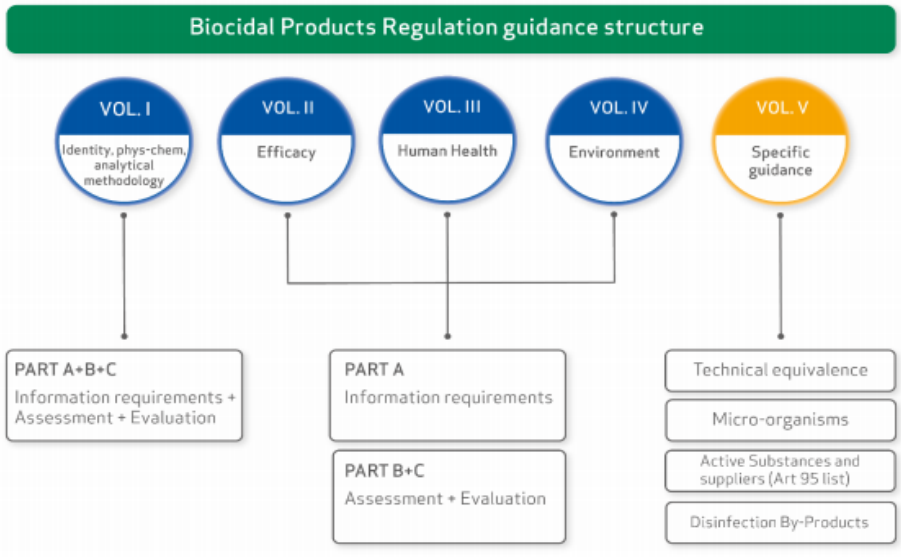
Disinfection By-Products

Disinfection by-products is another topic influenced by Member State initiatives, in this case by the Netherlands who have worked on harmonising an EU approach since 2011. The Competent Authorities (CAs) and the Technical Meetings (TM) decided that a risk assessment of DBPs should be conducted as part of the authorisation of the halogenated biocidal products. The TM agreed that a harmonised approach to such a risk assessment should be found for all halogenated disinfectants for Annex I inclusion (of the then BPD) and now active substance approval for the BPR, instead of postponing it to the national authorisation stage. Such a requirement changes the direction of active substances under review further delaying the process and places the responsibility for data generation disproportionately on a smaller number of companies (review programme participants).

2. Guidance Documents

Due to the wide scope of the BPR and the wide variation of efficacy, exposure and risks of biocidal products, the general rules provided in the BPR and its Annexes are specified in guidance in order to promote efficient and harmonised implementation of the regulation. The aim of the Guidance is to provide detailed and practical direction on which study data and other information should be submitted, when applying for active substance approval and product authorisation. Guidance is available to both Applicants and MSCA Evaluators.

The BPR sets out the broad criteria necessary for the approval of active substances and biocidal products containing those substances. The technical requirements needed to fulfil these criteria are detailed in formal guidance documents and other technical advice (such as the Technical Agreements for Biocide - TAB) which is published by ECHA. Guidance on Information Requirements are provided in Part A of the guidance and the Assessment and Evaluation of information in Part B +C guidance. The complete ECHA guidance series (to date) in support of the BPR is shown below:



[7] CA-Sept15-Doc.6.4 - Note to BPC EWP

The BPR guidance was developed based on the Technical Notes for Guidance (TNsG) that existed under the BPD. Much of the guidance remains unchanged, although it has been reformatted into a slightly more readable format in the current ECHA documents.

The main differences are:

- The term information requirement is used instead of data requirement. The new term reflects the fact that applicants do not in all cases need to supply data originating from studies, information from other sources being acceptable.
- Harmonisation with Guidance from other legal frameworks, for example REACH (Regulation (EC) No 1907/2006) is referred to for definitions and data waiving criteria.
- Core data requirements have been modified and certain long-term animal studies are only required when necessary.
- The BPR also allows for the adaptation of information requirements based on exposure as well as the use of techniques such as read-across, (Q)SAR and calculation methods.
- It is possible to provide a reduced data package on a case-by-case basis when applying for product authorisation, taking into account the nature of the product and the expected level of exposure.

The above descriptions point towards a degree of flexibility in providing information to support applications. However, in the case of active substance approval this should be seen in the context of BPR Article 6(2), which states that "*sufficient data shall be provided in order to make it possible to determine whether an active substance meets the criteria referred to in Article 5(1) or Article 10(1), if required by the evaluating competent authority under Article 8(2)*".

To establish exclusion criteria under Article 5(1) information concerning carcinogenicity (C), mutagenicity (M) and reproductive toxicity (R), in addition to information on endocrine disrupting (ED) potential and environmental persistence (P), bioaccumulation (B) and toxicity (T) are required. The need to conclude CMR properties and the level of classification under CLP creates a very high threshold to waive the data needed for these endpoints. This represents a fundamental change introduced by the BPR where an absence of data can no longer be accommodated by using additional safety factors in a risk assessment to account for uncertainty.

The clear consequence of not providing information to conclude Article 5(1) exclusion criteria is non-approval. An example here is the insecticide empenthrin, which was not approved for PT18 based on the absence of a 2-year carcinogenicity study[8]. The waiver submitted in place of study data was rejected, in part, because (Q)SAR was seen as not convincing for the lack of alerts for carcinogenicity.

The outcome for empenthrin underlines that study data are key to establishing substance endpoints. The difficulty comes in balancing the aims of the BPR to reduce animal testing and the use of the precautionary principle that underpins the regulation (Recital 3... "*This Regulation should be underpinned by the precautionary principle to ensure that the manufacturing and making available on the market of active substances and biocidal products do not result in harmful effects on human or animal health or unacceptable effects on the environment")*.

3. Exposure Assessment

An active substance shall be approved for an initial period not exceeding 10 years if at least one biocidal product containing that active substance may be expected to meet the criteria laid down in Article 19(1)(b) – the so called, one safe use principle. The criteria in Article 19(1)(b) stipulate (briefly) that products should be (i) sufficiently effective; (ii) have no unacceptable effects on the health of humans or animals and iii) have no unacceptable effects on the environment, including any impact on non-target organisms.

[8] Biocidal Products Committee (BPC) Opinion on the application for approval of the active substance: Empenthrin Product type: 18 - ECHA/BPC/182/2017. Adopted 13 December 2017.

Exposure assessment of the use of biocides provides significant information to determine what is considered acceptable and provides what is perhaps the largest area of uncertainty and controversy within the BPR. Biocides have a wide use pattern with many different uses, users and possibilities for exposure for humans and the environment.

Human Heath

Human health exposure assessments are guided by the opinions of Human Exposure Expert Group (HEEG – see Appendix 1) and the Ad hoc Working Group on Human Exposure (see Appendix 2) both of which prepare recommendations on issues concerning human exposure for which a harmonised approach is desirable. The accompanying ECHA guidance document - Biocides Human Health Exposure Methodology (365 pages) - is also available.

The information provided by these sources must be read together as multiple options exist when trying to model exposure scenarios and selecting which option is likely to be acceptable to evaluating Authorities is often unclear.

The opinions available from HEEG and the Ad hoc Working Group are complex, providing in many cases detailed technical background to the issues in question. Summary documents such as 'Recommendation No. 6 of the BPC Ad hoc Working Group'[9] have the highest value giving a more user-friendly overview of the available models and example scenarios for each PT where the model is applicable. Transferring these models into simple downloadable Excel calculators, would simplify the preparation and evaluation of dossiers and facilitate a more harmonised approach to risk assessment. Currently, these calculators are only available for a limited number of scenarios (an example case being the RISKOFDERM model).

In general, exposure models consider what are described as 'realistic worst-case scenarios', but in many cases, the calculated exposures actually represent extreme scenarios. This occurs because (each time) the worst-case value for individual components of the model is used.[10]

The outcome of risk assessments determine whether active substances may or may not be approved, or products authorised, but such decisions must consider the likelihood that the modelled exposure scenarios will occur in reality (e.g. PT6 - a child touching wet painted surfaces on a daily basis).

If models identify risk, the use of appropriate labelling should be an adequate measure to limit exposure and still permit approval of active substances and authorisation biocidal products (e.g. specifying professional only use in the event that risk is identified for infants).

Use instructions are an accepted feature of products in general and it should be a default assumption that users comply with these instructions. Regulatory decisions should not be based solely of risk identified for isolated or extremely rare scenarios (e.g. PT21 - toddlers exposed to wet paint by climbing on a boat in the garden) that could reasonably be avoided by appropriate use instructions.

Environment

Environmental exposure assessments are guided by emission scenario documents (ESDs) which are used to estimate the initial release of substances from biocidal products (or treated materials) to the environment. ESDs are available for each Product Type and consist of written guidance that include calculation methods to model exposure. Many of these documents are old, pre-dating the BPR, but recently a number of accompanying Excel spreadsheet tools have been added[11] by ECHA that help, if not necessarily simplify, the task of modelling exposure.

[9] Recommendation No. 6 of the BPC Ad hoc Working Group' on Human Exposure Methods and models to assess exposure to biocidal products in different product types'

[10] For example, the HEEG Opinion 'An approach to identification of worst-case human exposure scenario for PT6' (Section 3.1) - here exposure is determined by: the a.s. concentration in the product; the amount of the a.s. deposited on the surface; the likelihood of contact between consumer and the surface; the intensity, frequency and duration of such contact and for volatile substances, the ventilation rate. Worst case values are given for each component of the model which cummulatively results in highly unrealistic scenarios.

[11] Available for all PTs except PT3, PT11. PT12, PT16, PT17 and PT20 at the time of writing.

Assessment reports often cite precedent set by earlier substance evaluations and some of the decisions taken are captured in the Technical Agreements for Biocides (TAB), which is divided into separate documents addressing Chemistry, Efficacy, Toxicology and Environmental issues, as well as 'Cross-Cutting' issues. Whilst this is helpful, it follows the 'learning by doing' approach that has caused significant uncertainty for ongoing evaluation.

Environmental exposure assessment involves the estimation of release based on assumptions of how products are used and a common observation from those responding to the Survey is that exposure assessments are too conservative and the 'precautionary principle' is applied in a manner that simply selects the worst-case each time a choice of values is needed. As models require multiple inputs these worst-case choices are compounded, with the risk of taking the assessment beyond anything that might be considered proportional and realistic.

Appendix 1 – HEEG Opinions

HEEG opinion 1 - Mixing loading model 7 alternatives, Annex v2.2.1 – Calculator for RISKOFDERM Dermal Model

HEEG opinion 2 - Potential & Actual Hand Exposure

HEEG opinion 3 - Use of ConsExpo for the Exposure Assessment for Professional Users

HEEG opinion 4 - Amendment of TNsG on Human exposure to biocidal products Antifouling painting model

HEEG opinion 5- Human exposure assessment to biocidal products used in metalworking fluids (PT13) This HEEG opinion has been replaced by Recommendation 7 of the Ad hoc Working Group on Human Exposure Recommendation 7 – Professional exposure PT13

HEEG opinion 6 - Harmonising the use of new and old versions of the TNsG on human exposure and of BEAT

HEEG opinion 7 - Choice of secondary exposure parameters for PTs 2, 3 and 4

HEEG opinion 8 - Defaults and appropriate models to assess human exposure for dipping processes (PT 8)

HEEG opinion 9 - Default protection factors for protective clothing and gloves

HEEG opinion 10 - Harmonising the number of manipulations in the assessment of rodenticides (anticoagulants)

HEEG opinion 11 - Exposure model Primary exposure scenario - washing out of a brush which has been used to apply a paint, Annex - General exposure calculator for washing out of brushes

HEEG opinion 12 - Harmonised approach for the assessment of rodenticides (anticoagulants)

HEEG opinion 13 - Assessment of inhalation exposure of volatilised biocide active substance

HEEG opinion 14 - An approach to identification of worst-case human exposure scenario for PT6

HEEG opinion 15 has been replaced by HEAdhoc Recommendation 17

HEEG opinion 16 - Biocidal products: model for dipping of hands/forearms in a diluted solution

HEEG opinion 18 - For exposure assessment for professional operators undertaking industrial treatment of wood by fully automated dipping

Appendix 2 – Ad-Hoc Human Exposure WG Opinions

Recommendation 1 - Hand disinfection PT1 [PDF]

Recommendation 2 - Mopping and wiping time PT2 [PDF]

Recommendation 3 - Spraying models low pressure downward uses PT18 [PDF]

Annex - Studies with spraying applications PT18 [XLS]

Recommendation 4 - Cleaning spray equipment PT21 [PDF]

Recommendation 5 - Toddler scenario PT21 [PDF]

Recommendation 6 - Methods and models – version 4 [PDF]

Annex - PT18 professional exposure [XLSX]

Recommendation 7 - Professional exposure PT13 [PDF]

Recommendation 8 - Consumers protection factor from clothing[PDF]

Recommendation 9 - Professional hand disinfection in hospitals [PDF]

Annex - Inhalation exposure calculation ConsExpo [XLS]

Recommendation 10 – Paints non-professional application by brushing and rolling[PDF]

Recommendation 11 - Proposal for harmonisation PT19 assessment - version 2.1[PDF]

Recommendation 12 - Default values for indoor Transfer Coefficient[PDF]

Recommendation 13 - Teat Disinfection Products for Veterinary Hygiene (PT3)[PDF]

Recommendation 14 - Default human factor values for use in exposure assessments for biocidal products[PDF]

Recommendation 15 - Harmonisation of PT2 small surface disinfection exposure scenarios[PDF]

Recommendation 16 - Applicability of ConsExpo for water based disinfectants [PDF]

Annex - Modelling approaches used for calculations [XLS] (The numerical solution of the differential equations requires Visual Basic. Opening the attached document might display a warning message about the included macros.)

Recommendation 17 - Occupational exposure during application and removal of antifouling paints