Vitenskapskomiteen for mat og miljø
Norwegian Scientific Committee for Food and Environment

VKM Bulletin 2024: 04

VKM's methodology document for health and environmental risk assessments for use in the Panel on Plant Protection Products

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12.06.2024

ISSN: 2704-1689
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Cover image: Colourbox

Suggested citation: VKM, Marianne Stenrød, Esther Bloem, Nana Yaa Boahene, Tor Fredrik Holth, Mette Helen Bjørge Müller, Elise Rundén Pran, Christian Vogelsang, Tim Hofer (2024). VKM's methodology document for health and environmental risk assessments for use in the Panel on Plant Protection Products. Scientific Opinion of the Panel on Plant Protection Products of the Norwegian Scientific Committee for Food and Environment. VKM Bulletin 2024:04, ISSN: 2704-1689. Norwegian Scientific Committee for Food and Environment (VKM), Oslo, Norway.

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Preparation of the opinion

The Norwegian Scientific Committee for Food and Environment (Vitenskapskomiteen for mat og miljø, VKM) appointed a project group to draft the opinion. The project group consisted of 7 VKM members from the Panel on Plant Protection Products (one member had to leave the project group early in the project) and 1 VKM staff. The Committee, by the Panel on Plant Production Products, assessed and approved the final opinion.

Authors of the opinion

The authors have contributed to the opinion in a way that fulfils the authorship principles of VKM (VKM, 2019). The principles reflect the collaborative nature of the work, and the authors have contributed as members of the project group and/or the VKM Panel on Plant Protection Products.

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Acknowledgement

VKM would like to thank Christine L. Parr (VKM staff) for her contribution to Chapter 2, Methodology and data.

Competence of VKM experts

Persons working for VKM, either as appointed members of the Committee or as external experts, do this by virtue of their scientific expertise, not as representatives for their employers or third-party interests. The Civil Services Act instructions on legal competence apply for all work prepared by VKM.

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Summary

Background:

This work is a self-initiated assignment by the Panel on Plant Protection Products (PPPs) of the Norwegian Scientific Committee for Food and Environment (VKM). The main aim of the task was to update and expand the methodology document of the panel that has been in use since 2012 to reflect current regulations and practice, to ensure the quality of future risk assessments. Notably, Norway adopted the European Union (EU) regulations on pesticides in a new regulation; FOR-2015-05-06-455 (Forskrift om plantevernmidler, 2015) for PPPs in the summer of 2015, since Norway through the EEA agreement uses EUs approval scheme for the use of PPPs. The previous methodology document did not reflect these changes.

Method:

VKM appointed a project group consisting of 6 VKM members, and 1 VKM staff to draft the document. The project group employed a strategic and semi-systematic approach by compiling a working document (Appendix I) for the retrieval and compilation of the information needed regarding new data requirements stemming from current regulations for PPPs primarily in the EU. Current methods and method-related guidelines for risk assessments of PPPs regarding human health and environmental risks were also included. The same approach was taken to include data requirements and guidelines for biocides in the current document.

Findings:

The major updates by themes are the following:

- General
    - The document refers to the current version (last updated September 2023) of the Guidance document on work-sharing in the northern zone in the authorization of plant protection products, for a detailed overview of the specific requirements set out for Norway or jointly for the Northern zone countries. Norway joined this collaboration as a full partner upon the adoption of the EU PPP regulations in 2015.
    - Regulations and guidance regarding biocides, novel types of pesticides (low risk, nano- etc.), adapted/simplified approval/risk assessment for microbials (2022) and proposed data requirements for safeners and synergists among others are new additions to the current document.

- Human toxicology
    - Guidance document outlining the scientific criteria for hazard identification of substances with endocrine disrupting properties in pesticides and biocides based on Commission Delegated Regulation (EU) 2017/2100 for biocidal products and Commission Regulation (EU) 2018/605 for PPPs.
    - Opening for use of alternative methods to decrease toxicological testing in animals.
    - A harmonized guidance on the assessment of non-dietary exposure of operators, workers, residents, and bystanders to PPPs.
- Environmental fate and behaviour
    - The impact of Norwegian soil and climate conditions on the fate and behaviour of pesticides in the environment have been updated with more recent investigations on this topic. The Norwegian Food Safety Authority changed their requirements for regulatory modeling scenarios November 2023.
    - Information about the fate of pesticides in wastewater treatment plants and the impact of pesticides on drinking water purification processes, have been included.
- Ecotoxicology
    - Introduction and implementation of specific protection goals (SPGs) as well as a tiered approach regarding aquatic risks due to toxicity.
    - In 2023, EFSA published a revised guidance document covering honeybees, bumblebees, and solitary bees. The endorsement procedure of the revised guideline is in progress. Regulation updates is expected to be completed at the earliest spring 2024.
    - The guidance document on risk assessment for birds and mammals from 2009, was updated in 2023. However, the updated guidance is not yet implemented. The new guidance document outlines a tiered risk assessment scheme covering dietary exposure, exposure via secondary poisoning and exposure via intake of contaminated water. Also, a calculator tool is available.

Conclusions:

The current document is to serve as a reference document for the risk assessment work of the VKM PPP panel, and at present its content reflects the regulatory framework in sufficient accuracy and detail. When performing risk assessments, the available scientific literature will be reviewed for the topic in question and, hence, any lacks in this methodology document will not impact the quality of any future risk assessments performed.

Key words: VKM, (benefit and) risk assessment, Norwegian Scientific Committee for Food and Environment, Plant Protection Products, biocides and methodology

Sammendrag på norsk

Bakgrunn:

Arbeidet er et selvinitiert oppdrag fra faggruppen for plantevernmidler i Vitenskapskomiteen for mat og miljø (VKM). Hovedmålet med oppgaven var å oppdatere og utvide metodedokumentet som har vært i bruk i faggruppen siden 2012 for å gjenspeile gjeldende regelverk og praksis og for å sikre kvaliteten på fremtidige risikovurderinger. Norge vedtok EUs regelverk for plantevernmidler i en ny forskrift; FOR-2015-05-06-455 (Forskrift om plantevernmidler, 2015) for plantevernmidler sommeren 2015, siden Norge gjennom EØS-avtalen benytter EUs godkjenningsordning for bruk av plantevernmidler. Det forrige metodedokumentet reflekterte ikke disse endringene.

Metode:

VKM satte ned en prosjektgruppe bestående av 6 VKM-medlemmer og 1 fra sekretariatet i VKM til å utarbeide dokumentet. Prosjektgruppen benyttet en strategisk og semi-systematisk tilnærming ved å utarbeide et arbeidsdokument (vedlegg I) for innhenting og sammenstilling av nødvendig informasjon om nye datakrav som stammer fra gjeldende regelverk for plantevernmidler primært i EU. Gjeldende metoder og metoderelaterte retningslinjer for risikovurdering av plantevernmidler med hensyn til menneskers helse og miljørisiko ble også inkludert. Samme tilnærming ble lagt til grunn for å inkludere datakrav og retningslinjer for biocider i det nåværende dokumentet.

Resultater:

De viktigste oppdateringene etter temaer er følgende:

- Generelt
    - Dokumentet viser til gjeldende versjon (sist oppdatert september 2023) av veiledningsdokumentet om arbeidsdeling i nordlig sone ved godkjenning av plantevernmidler, for en detaljert oversikt over de spesifikke kravene som stilles for Norge eller i fellesskap for landene i nordlig sone. Norge sluttet seg til dette samarbeidet som fullverdig partner da EUs regelverk for plantevernmidler ble vedtatt i 2015.
    - Forskrifter og veiledning om blant annet biocider, nye typer plantevernmidler (lavrisiko, nano- etc.), tilpasset/forenklet godkjenning/risikovurdering for mikrobielle stoffer (2022) og forslag til datakrav for ulike typer

tilsetningsstoffer (safeners and synergists) er nye tillegg til gjeldende dokument.

- Human toksikologi
    - Veiledningsdokument som beskriver de vitenskapelige kriteriene for fareidentifisering av stoffer med hormonforstyrrende egenskaper i plantevernmidler og biocider basert på «Commission Delegated Regulation (EU) 2017/2100» for biocidprodukter og «Commission Regulation (EU) 2018/605» for plantevernmidler.
    - Åpning for bruk av alternative metoder for å redusere toksikologisk testing hos dyr.
    - En harmonisert veiledning for vurdering av yrkeseksponering og ikke-kostholdeksponering for operatør, arbeidere, beboere og forbipasserende for plantevernmidler.
- Egenskaper og skjebne i miljøet
    - Virkningen av norske jord- og klimaforhold på plantevernmidlers nedbrytning og spredning i miljøet er oppdatert med nyere undersøkelser om temaet. Mattilsynet endret sine krav til regulatoriske modelleringsscenarier november 2023.
    - Informasjon om nedbrytningen av plantevernmidler i renseanlegg og virkningen av plantevernmidler på drikkevannsreneprosesser er inkludert.
- Økotoksikologi
    - Implementering av spesifikke beskyttelsesmål (SPG) samt en trinnvis tilnærming til vurdering av risiko i akvatisk miljø.
    - Revidert veiledning i 2023 som omfatter honningbier, humler og solitære bier. Godkjenningsprosedyren for den reviderte veilederen, samt tilknyttede og nødvendige endringer av regelverket, pågår.
    - Veilederen for risikovurdering for fugl og pattedyr fra 2009, ble oppdatert i 2023. Den oppdaterte veiledningen er imidlertid ennå ikke implementert. Det nye veiledningsdokumentet skisserer en trinnvis risikovurderingsordning som dekker eksponering via mat, eksponering via sekundær forgiftning og

eksponering via inntak av forurenset vann. Det finnes også et kalkulatorverktøy.

Konklusjoner:

Dette dokumentet skal fungere som et referansedokument for faggruppen for plantevernmidler i VKMs risikovurderingsarbeid, og innholdet gjenspeiler i dag regelverket med tilstrekkelig nøyaktighet og detaljering. Ved risikovurderinger vil tilgjengelig vitenskapelig litteratur bli gjennomgått for det aktuelle temaet, og eventuelle mangler i dette metodedokumentet vil derfor ikke påvirke kvaliteten på eventuelle fremtidige risikovurderinger som utføres.

Nøkkelord: VKM, (nytte- og) risikovurdering, Vitenskapskomiteen for mat og miljø, plantevernmidler, biocider og metodikk

Abbreviations and glossary

Abbreviations

AS	active substance
AF	Assessment Factor
AGD	Aquatic Guidance Document
AUC	Area Under the Curve
BCF	Bioconcentration Factor
BMF	Biomagnification Factor
CA	Concentration Addition
ECHA	European Chemicals Agency
ECx	Concentration where x % effect was observed/calculated
EFSA	European Food Safety Authority
EPPO	European and Mediterranean Plant Protection Organization
ERO	Ecological Recovery Option
ETO	Ecological Threshold Option
ETR	Exposure-Toxicity Ratio
FOCUS	FOrum for the Co-ordination of pesticide fate models and their USe
JRC	Joint Research Centre
Log K_{oa}	Partitioning coefficient octanol-air
Log K_{ow}	Partitioning coefficient octanol-water
LRP	Low risk pesticide
MRR	Maximum Recommended Application Rate
NAMs	New approach methodologies
NOEC	No Observed Effect Concentration
PIEC	Predicted Initial Environmental Concentration
PEC	Predicted Environmental Concentration
PPP	Plant Protection Product
ProbRA	Probabilistic risk assessment
(Q)SAR	(Quantitative) Structure-Activity Relationship
RA	Risk Assessment
RAC	Regulatory Acceptable Concentration
SETAC	Society for Environmental Toxicology and Chemistry
SPG	Specific Protection Goal
SSD	Species Sensitivity Distribution
SW	Surface water
TD/TK	Toxicodynamic/toxicokinetic
TFD	Terrestrial Field Studies
TWA	Time weighted average
VKM	Norwegian Scientific Committee for Food and Environment

Glossary

Biocide: A chemical substance or microorganism used to control unwanted organisms that are harmful to human or animal health or to the environment, or that cause damage to human activities. These harmful organisms include pests (e.g. insects, rats or mice) and microorganisms (e.g. bacteria, viruses, mould). Biocidal products include among others: insecticides (except those used for plant protection purposes which are regulated by Regulation (EU) No 1107/2009), insect repellents, disinfectants, preservatives for materials such as wood, plastics and fibres, anti-fouling paints for the protection of ship hulls.

Exposure profile: The course of time of the concentration on a relative concentration scale (an effect study is usually carried out at different concentration levels but with the same exposure profile).

Low risk pesticide: An active substance can be approved as a low-risk substance if it meets the regular approval criteria and in addition meets the low-risk criteria as specified in Annex II, point 5 of Regulation (EC) 1107/2009. An active substance shall not be considered of low risk where it is or has to be classified in accordance with Regulation (EC) No 1272/2008 as at least one of the following: carcinogenic, mutagenic, toxic to reproduction, sensitising chemicals, very toxic or toxic, explosive, corrosive. It shall also not be considered as of low risk if: persistent (half-life in soil is more than 60 days), bioconcentration factor is higher than 100, it is deemed to be an endocrine disrupter, or it has neurotoxic or immunotoxic effects.

Metabolite: Any metabolite or a degradation product of an active substance, safener or synergist, formed either in organisms or in the environment (thus also including oxidation products which may have a larger molecular mass than the parent substance) (EFSA, 2012).

Nano-pesticides: plant protection products where nanotechnology is employed to enhance the efficacy or reduce the environmental footprint of a pesticide active ingredient (Kookana et al., 2014).

Plant Protection Products (also referred to as 'pesticides') are products in the form in which they are supplied to the user, consisting of, or containing active substances, safeners or synergists, and intended for one of the following uses:

- protecting plants or plant products against all harmful organisms or preventing the action of such organisms, unless the main purpose of these products is considered to be for reasons of hygiene rather than for the protection of plants or plant products (e.g. fungicides, insecticides);

- influencing the life processes of plants, such as substances influencing their growth, other than as a nutrient (e.g. plant growth regulators, rooting hormones);
- preserving plant products, in so far as such substances or products are not subject to special Community provisions on preservatives (e.g. extending the life of cut flowers);
- destroying undesired plants or parts of plants, except algae unless the products are applied on soil or water to protect plants (e.g. herbicides/weedkillers to kill actively growing weeds);
- checking or preventing undesired growth of plants, except algae unless the products are applied on soil or water to protect plants (e.g. herbicides/weedkillers preventing the growth of weeds).

Risk assessment is a specialized field of applied science that involves reviewing scientific data and studies to evaluate risks associated with certain hazards. It involves four steps: hazard identification, hazard characterization, exposure assessment and risk characterization.

Background

The Panel on Plant Protection Products (PPPs) seeks to update and expand our methodology document that has been in use since 2012 to reflect current regulations and practice, and to ensure the quality of future risk assessments. The purpose of the methodology document published in 2012 was to describe the methods used by the Norwegian Food Safety Authority for use as background documentation for the Norwegian Scientific Committee for Food and Environment (VKM), and to describe criteria that VKM (Panel on PPPs) uses as basis for risk assessment of PPPs (VKM, 2012). The methodology document was intended to be a dynamic document that reflects current practice, in line with changes in regulations and the supply of new knowledge.

Norway adopted the European Union (EU) regulations on pesticides in a new regulation (Forskrift om plantevernmidler, 2015) for PPPs in the summer of 2015, since Norway through the EEA agreement uses EUs approval scheme for the use of PPPs.

VKM shall, in accordance with one of its main objectives in its strategy document 2021-2024, ensure an independent, high-quality base of knowledge by:

- Developing methods and contributing to international methodology work
- Following international standards and guidelines

This will help ensure VKM's assessments are verifiable and based on updated and relevant knowledge. Updating the methodology document of 2012 is thus vital to ensure the quality of future risk assessments in the Panel on PPPs. The biocide regulation is also relevant because many of the same active substances are currently approved (or have been approved) both as pesticides and biocides. Although with very different areas and methods of use, certain product categories and use areas for biocides may cause co-occurrence of biocides and pesticides in the same exposure environment. Hence, methodology for risk assessment of biocides will also be included in the updated document.

Terms of reference

The Panel will update and expand the methodology document published in 2012 with new data requirements stemming from current regulations and terminology for PPPs, as well as with new/updated methods and method-related guidelines for risk assessments of these products regarding human health and environmental risks.

The update will be written in English (The 2012 version is in Norwegian).

1 Introduction

The current methodology document is intended for use as a reference document in VKM's Panel for PPPs. The document consists of two main sections (human and environmental) on the risk assessment (RA) methodologies available for PPPs as well as biocides regarding human health and environmental exposures mainly in the EU. Norway, via the EEA agreement employs EUs approval scheme for the use of PPPs, and thus adopted the EU regulations on pesticides in a new regulation; FOR-2015-05-06-455 (Forskrift om plantevernmidler, 2015) for PPPs in the summer of 2015. Notably, RA of pesticides is a complex task that encompasses various disciplines; thus, a multidisciplinary approach is required. Here, we attempt to capture the core elements and minimum requirements needed for the RA methodology in the EU. Figure 1 is a schematic representation of the different sections of the RA process for PPPs.

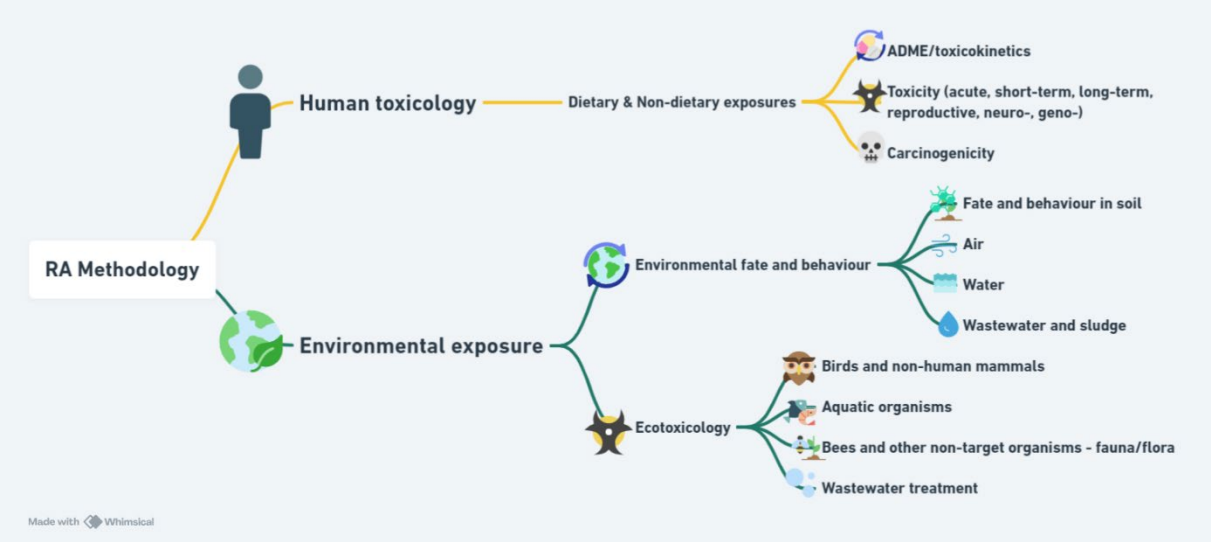

Figure 1: A schematic representation of the different sections of the RA process for PPPs

In brief, mammalian toxicology is limited to human dietary and non-dietary exposures in the following subdivisions/endpoints: absorption, distribution, metabolization, excretion (ADME)/toxicokinetics, acute toxicity, short-term toxicity, genotoxicity, long-term toxicity and carcinogenicity, reproductive toxicity, neurotoxicity, and other toxicological endpoints/studies that may be relevant.

Environmental exposure is divided into:

- Environmental fate and behaviour with the following subdivisions: route and rate of degradation in soil, adsorption, desorption and mobility in soil, fate and behaviour in water and impact on water treatment procedures, fate and behaviour in air.
- Ecotoxicology with the following subdivisions: birds and non-human mammals, aquatic organisms, bees and non-target arthropods, earthworms, and other soil non-target organisms (macro and micro), as well as other non-target organisms (flora and fauna), and sewage treatment

Active substances are assessed and authorized by the Standing committee on Plants, Animals, Food and Feed (SCoPAFF) jointly for the member states in the EU/EEA. All EU/EEA countries are represented in the committee, presided by a European Commission representative. Active substances, and plant protection products, must fulfil the approval criteria laid down in Regulation (EC) No 1107/2009. (Commission Regulation (EC) No 1107/2009, 2009), [note: these regulations can contain several annexes (e.g. I, II, III, IV)]. All approved active substances are listed in Implementing Regulation (EU) No 540/2011 and in the EU Pesticides Database. Plant protection products are assessed and approved through a zonal assessment but must be applied for and nationally authorized in the relevant state. The Norwegian Food Safety Authority therefore cooperates with the EU member states, as well as Nordic and Baltic member states (the northern zone: Norway, Sweden, Denmark, Finland, Estonia, Latvia, Lithuania and Iceland). One of the countries acts as zonal rapporteur member state (zRMS), performing the assessment, whereas the others comment on the assessment. Norway has several national environmental requirements, including risk assessment for six different surface water scenarios. See the Northern Zone Guidance Document; A1 (Northern Zone, 2023).

Approved active substances in PPPs and biocides are regarded as registered under REACH and are subject to classification and labelling; CLP regulation 1272/2008 (Commission Regulation (EC) No 1272/2008, 2008) regarding hazard assessment (when a pesticide active substance is submitted to the peer review assessment by EFSA, a CLH report should also be submitted by the Member State Competent Authority to ECHA, so that the two assessment processes are run in parallel). Data requirements and relevant guidance documents are discussed with applicants (industry) at pre-submission meetings with EFSA. Biocides need to comply with regulations 528/2012 and 2021/525 (Commission Delegated Regulation (EU) 2021/525, 2020; Commission Regulation (EU) No 528/2012, 2012).

2 Methodology and Data

The following sections describe the strategy for retrieving and compiling the information used under each of the objectives.

2.1 Data and information gathering

2.1.1 Retrieval and review of method-related parts of EU-regulations (objective 1a)

2.1.1.1 Primary information sources

To identify changes data/information requirements in EU regulations of PPPs and biocides since 2012, updated regulations were retrieved from the EU, EFSA, and ECHA websites.

The key documents on regulation of PPPs on the EU website can be found here:

https://food.ec.europa.eu/plants/pesticides/legislation-plant-protection-products-ppps_en

(Legislation on Plant Protection Products, 2023)

https://food.ec.europa.eu/plants/pesticides/micro-organisms_en (Micro-organisms used in plant protection products, 2023)

https://food.ec.europa.eu/plants/pesticides_en (Pesticides, 2023)

Further, guidelines and supporting documents on active substance and plant protection products can be found here: https://webgate.ec.europa.eu/dyna2/pgd/documents (Guidelines and supporting documents on Active Substances and Plant Protection Products, 2024). Notably, these documents have not been reviewed in full and is listed here as a key source of updated information.

Additionally, EFSA has a specific website that assembles the requisite documents on EU regulations for pesticide evaluations; https://www.efsa.europa.eu/en/applications/pesticides/regulationsandguidance (Pesticide evaluations: regulations and guidance, 2024). We went through the regulatory framework for data requirements and test methodologies needed for risk assessment and approval of PPP from 2005 to present since some existing regulations date as far back as 2005.

The Norwegian Food Safety Authorities have also late 2023 established a website for easier access to the regulations and guidance documents relevant for the PPP authorization process for Norway (https://www.mattilsynet.no/en/plants/authorisation/veiledere-guidance-documents-plantevernmidler).

Regarding biocides, the key documents are located on this EU website: https://health.ec.europa.eu/biocides/key-documents_en (Biocides, 2023)

In addition, ECHA's Biocidal Products Committee (BPC) regularly publishes Technical Agreements for Biocides (TAB): https://webgate.ec.europa.eu/s-circabc/faces/jsp/extension/wai/navigation/container.jsp (S-CIRCABC, 2024)

We screened the ECHA website primarily for themes that are not covered by the afore-mentioned websites regarding data requirements and test methodologies needed for risk assessment and approval of active substances in biocidal products: https://echa.europa.eu/en/information-on-chemicals/active-substance-suppliers (ECHA: Information on biocides, 2024).

2.1.1.2 Eligibility criteria

We retrieved regulations regarding the themes listed under scope in the protocol, Appendix I, section 3.1.

2.1.1.3 Mapping of changes since 2012

We have gone through the methodology document from 2012 to retrieve data requirements and any additional information that is still applicable based on current EU regulations. These were transferred to the current methodology document, whereas data requirements that are no longer applicable due to amendments in regulations or outdated methodologies were excluded.

As stated earlier in section 1, in the summer of 2015, Norway adopted EU regulations on pesticides in a new regulation for PPPs (Forskrift om plantevernmidler, 2015); since Norway through the EEA agreement uses the European Union's approval scheme for the use of these products. It is thus needful to expand the methodology document with existing EU regulations, some of which dates to 2005, for a holistic overview.

2.1.2 Retrieval and review of current methodology guidelines/guidance documents for risk assessment according to EU regulations (objective 1b)

2.1.2.1 Primary information sources

The PPP and biocide EU regulations specify study/data/information requirements by the registrants (industry). Often (not always), shall studies be performed according to mentioned OECD test guidelines (TGs) and be of good laboratory practice (GLP) quality. The OECD guidelines for testing of chemicals are unique tools for assessing the potential effects of chemicals on human health and the environment, being split into five sections: Section 1: Physical-Chemical properties; Section 2: Effects on Biotic Systems; Section 3: Environmental fate and behaviour; Section 4: Health Effects and Section 5: Other Test Guidelines. Thus, regarding information on validated test guideline methods, the OECD website will be employed (OECD Guidelines for the Testing of Chemicals, 2024).

Guidance documents additionally provide recommendations on certain topics:

EFSA has a specific website that assembles EU scientific guidance documents for pesticide evaluations (Pesticide evaluations: regulations and guidance, 2024). We went through the scientific guidelines /guidance documents for information / recommendations on current best practices regarding models and methodologies for risk assessment and approval of PPP from 2009 to present.

We screened the ECHA website primarily for scientific guidelines / guidance documents for information / recommendations on current best practices regarding models and methodologies for risk assessment and approval of biocides (ECHA: Information on biocides, 2024).

2.1.2.2 Mapping of changes since 2012

We went through the entire methodology document from 2012 to retrieve information that is still relevant on best practices regarding models and methodologies for risk assessment and approval of PPPs. These were transferred to the current methodology document, whereas information / recommendations that are no longer applicable based on updates in methodology guidelines / guidance documents were excluded.

As stated earlier in background, in the summer of 2015, Norway adopted EU regulations on pesticides in a new regulation for PPPs (Forskrift om plantevernmidler, 2015), since Norway through the EEA agreement uses the European Union's approval scheme for the use of these

products. It is thus needful to expand the methodology document with existing EU regulations, some of which dates to 2005, for a holistic overview.

2.1.3 Retrieval and review of national legislation and other international guidelines/guidance documents (Objective 2a)

2.1.3.1 Primary information sources for national legislation

For information and regulations regarding specific Norwegian conditions, the following databases and websites were screened: Lovdata.no (Forskrift om plantevernmidler, 2015. FOR 2015-05-06-455, accessible from https://www.lovdata.no, mattilsynet.no, miljødirektoratet.no, https://www.oecd.org/norway/.

2.1.3.2 Information sources for international guidelines

Regarding information on validated international test guidelines and methods, the Codex Alimentarius website was screened as deemed necessary for any additional information of relevance to the topics of interest (Codex Alimentarius, 2024).

2.1.3.3 Mapping of expansions to document

We went through the entire methodology document from 2012 to retrieve information on best practices regarding models and methodologies for risk assessment and approval of PPP. These were transferred to the current methodology document, whereas information / recommendations that were no longer applicable based on updates in methodology guidelines / guidance documents were excluded.

2.1.3.4 Handling of study records (objectives 1a, 1b, 2a)

An EndNote library was compiled for all relevant documents and sources of information obtained.

2.2 Literature search and selection

2.2.1 Scientific literature search (Objective 2b)

The purpose of the search for scientific review papers was to identify additional information and opinions regarding models and methodologies in current practice that will be useful in future risk assessments performed in the Panel.

2.2.1.1 Eligibility criteria

Studies eligible for inclusion under objectives 2b are described in table 2.2.1.1.

Table 2.2.1.1. Overview of eligibility criteria (objective 2b)

Context	Literature from research databases describing new and relevant RA methodologies not covered by EU regulations (see Appendix II- search strategy for details)
Language	Studies and documents in English, Norwegian or other Scandinavian language.
Date	Publications from 2012 onwards to search date
Type of publications	Review articles, and any additional reports that were not covered under previous sections.

2.2.1.2 Exclusion criteria

Table 2.2.1.2. Overview of exclusion criteria (objective 2b)

Context	Literature that falls outside the context described in the eligibility criteria
Language	Studies and documents not in English, Norwegian or other Scandinavian language.
Date	Publications before 2012

Type of publications	Primary studies, publications on genetically modified organisms, medicinal products, letter to editor, comments, conference abstract, posters, articles that do not deal with RA methodologies for pesticides and biocides.

2.2.1.3 Information and data sources

To answer objective 2b, specific search terms for review articles based on findings from objective 1a and b as well as an initial test search performed by an experienced librarian were employed. The following databases were searched for only reviews: Ovid Medline, Embase, Web of Science, the Cochrane Database of systematic reviews, and Epistemonikos.

Additional manual searches for relevant articles and grey literature that were missed by the main search were also performed in Google Scholar and other databases to strengthen the knowledge base of the assessment.

2.2.1.4 Search strategy

Specific search strategies were drafted in cooperation with an experienced librarian, who performed the literature searches, see appendix II for details.

Search terms for PPPs:

Pesticide, biocide, nano-pesticide, co-formulant, low risk pesticide, active substance.

Search terms for mammalian (human) health risk assessment

Hazard/risk identification /characterisation, single/repeated administration, exposure assessment, human/occupational exposure toxicity/toxicology, mammalian toxicology, threshold, health-based guidance values, (HBGL), maximum residue limit (MRL), no/lowest observable adverse effect level (NO(A)EL/LO(A)EL), benchmark dose (BMD), average daily intake (ADI), acute reference dose (ARfD), critical effects, oral intake, inhalation, dermal absorption, genotoxicity studies, toxicokinetics, acute toxicity, short-term toxicity, genotoxicity, long-term toxicity and carcinogenicity, reproductive toxicity, neurotoxicity.

Search terms for methodologies and models for qualitative/quantitative human health risk assessments:

Hazard Index, Monte Carlo risk assessment tools (MRCA), pesticide residue intake model (PRIMO), quantitative structure activity relationship (QSAR), probabilistic risk assessment.

Search terms for environmental risk assessment (ERA)

Environmental fate and behaviour: route and rate of degradation in soil, adsorption, desorption and mobility in soil, fate and behaviour in water, waterworks, and wastewater/sewage treatment plants/processes (wastewater and sludge), fate and behaviour in air, hazard/risk identification, risk characterisation, exposure assessment, models for qualitative/quantitative assessments, soil, air, surface water, ground water, runoff, mobility, leaching, biological/abiotic degradation, sorption, aged sorption, predicted environmental concentration (PEC), Predicted no-effect concentration (PNEC), biological effect marker/biomarker.

Ecotoxicology: birds and mammals, aquatic organisms, bees and non-target arthropods, earthworms, and other soil non-target organisms (macro and micro), as well as other non-target organisms (flora and fauna), and wastewater treatment - anaerobic digestion, nitrification (sewage treatment - impact on biological treatment processes), hazard/risk identification, risk characterisation, exposure assessment, models for qualitative/quantitative assessments, ecotoxicology, bioaccumulation factor (BAF), bioconcentration factor (BCF), biomagnification factor (BMF), no/lowest observable adverse effect concentration (NO(A)EC/LO(A)EC), toxicity equivalency factor/quotient (TEF/TEQ), species sensitivity distribution (SSD).

Search terms for methodologies and models for qualitative/quantitative ERAs:

FOrum for Co-ordination of pesticide fate models and their USe (FOCUS), The EXposure Analysis Modelling System (EXAMS).

2.2.1.5 Information and study records

Selection process / Screening of search results

Screening of titles and abstracts was undertaken pairwise (two reviewers) and blinded employing the Rayyan tool for systematic literature screening based on the set of inclusion and exclusion criteria agreed on by the pair and/or project group beforehand. Selected publications were exported to an Endnote library and distributed among members of the project group for their perusal. Additional individual searches were performed by project group members for the different themes where needed.

Data synthesis

Information on models, methods and approaches used for the regulatory, pre-authorization risk assessment of pesticides, biocides from the studied reviews and reports are described in the current report. Key challenges with these models, methods, and approaches and/or known knowledge gaps are commented and related to the risk assessment procedures currently employed by VKM.

3 Human toxicology

To ensure the safety of PPPs and biocides, various tests are required (data requirement specified in regulations) before such products reach the market. EU regulations 283/2013 on active substances in PPPs (Commission Regulation (EU) No 283/2013, 2013) and 284/2013 on PPPs; the product as whole, also non-active substances (Commission communication, 2013) states that testing in humans or non-human primates shall not be performed. Tests on vertebrate animals shall be undertaken only where no other validated methods are available. Alternative methods to be considered shall include in vitro and in silico methods (replacement). Reduction and refinement (3R principle) methods for in vivo testing shall be encouraged. However, for many endpoints regulatory accepted alternative methods are yet not available and animal studies frequently need to be performed. The oral route shall always be used if it is practical. All potentially adverse effects found during toxicological investigations (including effects on organs/systems such as the immune system, the nervous system, or the endocrine system) shall be reported. Reported critical effect thresholds (reference points), e.g. NOAEL (or calculated BMDL) values for repeated administration in rats/dogs, can be used for risk assessment (e.g. for derivation of acceptable daily intake (ADI) values of pesticides).

3.1 Toxicokinetics - ADME, bioaccumulation

The purpose of absorption, distribution, metabolism, and excretion (ADME) studies is to obtain information on blood and tissue concentrations of the active substance and relevant metabolites, for example around the time at maximal plasma concentration (T_{max}), to enhance the value of toxicological data generated in terms of understanding the toxicity studies. The main objective of the toxicokinetic data is to describe the systemic exposure achieved in animals and its relationship to the dose level and the time course of the toxicity studies. According to the PPP regulation, ADME studies are required for active substances, and shall be generated in short and long-term studies in relevant species.

The studies shall provide sufficient information about the kinetics of the active substance and its metabolites in relevant species after being exposed to single (low and high) dose, intravenous dose, and repeated (often low) dose. A key parameter is systemic bioavailability (F), obtained by comparison of the area under the curve (AUC) after oral and intravenous dosing. Other parameters include extent and rate of oral absorption, C_{max}, potential for bioaccumulation, plasma half-lives, distribution in major organs, tissues and blood cells, formed metabolites, excretion routes and rates, and extent of enterohepatic circulation. Comparative in vitro metabolism in animal and human material (microsomes or intact cell

systems) shall be performed to determine the relevance of the toxicological animal data. Depending on substance volatility and relevant exposure routes, also inhalation and dermal studies are possible/required. A commonly used test guideline is OECD TG 417 'Toxicokinetics' (2010) in which rats are the main species. Other species can also be considered (OECD, 2010). Data restricted to one in vivo test species (normally rat) may be all that is required as regards ADME after exposure by oral route.

Livestock feeding metabolism studies are generally also required, and OECD TG 503 'Metabolism in Livestock' is commonly followed in which metabolism in poultry (normally egg laying hens) and ruminants (normally lactating goats, sometimes pigs) are separately studied (OECD, 2007). Both TG 417 and TG 503 normally require administration of a radioisotope (commonly ^{14}C) labelled substance which facilitates mass balance determinations (OECD, 2007, 2010). Metabolism in rats is compared to that in livestock.

Bioaccumulation assessment (described below under Ecotoxicology/Aquatic organisms) begins with investigation of the active substance's physical-chemical properties. For lipophilic substances (log K_{ow}>3), test of bioconcentration(accumulation) in fish is often required using OECD TG 305 'Bioaccumulation in fish: aqueous and dietary exposure' (OECD, 2012). However, since it has become increasingly clear that fish, for several types of chemicals, is a poor model for bioaccumulation in air-breathing land-living mammals (humans, rats, pigs, horses, etc), a new tier-based bioaccumulation assessment strategy (tier I: physical-chemical properties such as log K_{ow} and log K_{oa}; tier II: metabolism (in vitro) investigation; III: tier in vivo testing in land living mammals) has been proposed (ECHA, 2022). For neutral hydrophobic organic substances, based on steady state conditions and fugacity as driving factor for bioaccumulation, approximate thresholds for whole-body elimination half-lives in rats (4 d) and humans (50 d) were calculated (ECHA, 2022) as mentioned in ECHA's 'Application of the CLP criteria - v6.0, 2024' (ECHA, 2024), ECHA's guidance documents R.7c 'Endpoint specific guidance'; v4.0, 2023 (ECHA, 2023a) and R.11 'PBT assessment'; v4.0, 2023 (ECHA, 2023b). Use of biomagnification factor (BMF) or trophic magnification factor (TMF) > 1 (at steady-state) are alternative parameters describing bioaccumulation. Depending on usage (flexible study design), TG 417; toxicokinetics in rats (OECD, 2010) can provide bioaccumulation relevant parameters such as blood plasma elimination half-life (note: there can be several phases: α-, β-, γ-, etc.), excretion rates, and percentage of substance in tissues at the end of the study.

3.2 Acute toxicity

The information generated through acute toxicity testing is of particular value in assessing hazards likely to arise in accident situations. The studies shall be sufficient to permit the

identification of effects following a single exposure to the active substance, and in particular to establish, or indicate: (a) the toxicity of the active substance; b) the time course and characteristics of the effects with full details of behavioural changes, clinical signs, where evident, and possible gross pathological findings at post-mortem; (c) the possible need to consider establishing acute reference doses (such as ArfD, aAOEL); (d) where possible mode of toxic action; and (e) the relative hazard associated with the different routes of exposure; 283/2013, Annex II (Commission Regulation (EU) No 283/2013, 2013). Additionally, the toxicity of the product as a whole (active substance and non-active substances) needs to be assessed, as well as the product relative to the active substance; 284/2013 (284/2013, 2013). While the emphasis shall be on estimating the toxicity ranges involved, the information generated shall also permit the active substance and product to be classified according to regulation 1272/2008 (CLP), where applicable (Commission Regulation (EC) No 1272/2008, 2008; ECHA, 2024).

Acute toxicity studies using animals shall not be required if the applicant can justify an alternative approach under Regulation (EC) No 1272/2008, where applicable (Commission Regulation (EC) No 1272/2008, 2008). For this purpose, acute toxicity of all components shall be provided or reliably predicted with a validated method.

3.2.1 Oral

Acute oral toxicity studies (common species is rat) administrate single high doses designed to identify death or serious signs of toxicity with emphasis on classification and labelling. EU regulation 283/2013 (active substances) lists examples of acceptable study guidelines, e.g. OECD TG 420 'Acute oral toxicity: fixed dose procedure', OECD TG 423 'Acute oral toxicity: acute toxic class method', OECD TG 425 'Acute oral toxicity: up-and-down procedure', and OECD TG 401 'Acute oral toxicity' (only acceptable, if performed before December 2002). For products, consideration shall be given to the possible effects of components on the toxic potential of the total mixture (Commission Regulation (EU) No 283/2013, 2013).

3.2.2 Dermal

The acute dermal toxicity of the active substance shall be reported unless waiving is scientifically justified (for example where oral LD_{50} is greater than 2 000 mg/kg). Both local and systemic effects shall be investigated. EU regulation 283/2013 mentions that OECD TG 402 'Acute Dermal Toxicity' as an acceptable study guideline (Commission Regulation (EU) No 283/2013, 2013). Findings of severe skin irritation (Grade 4 erythema or oedema) in the dermal study shall be used instead of performing a specific irritation study. For products,

consideration shall be given to the possible effects of components on the toxic potential of the total mixture.

For biocides (EU 528/2012), testing by the dermal route is necessary only if: inhalation of the substance is unlikely, or skin contact in production and/or use is likely, and either the physicochemical and toxicological properties suggest potential for a significant rate of absorption through the skin, or the results of an in vitro dermal penetration study (OECD TG 428) demonstrate high dermal absorption and bioavailability (Commission Regulation (EU) No 528/2012, 2012).

3.2.3 Inhalation

Requirement to perform acute inhalation toxicity studies depends on physical characteristics of the active substance and product, e.g. vapour pressure (> 1 × 10–2 Pa), powder particle size (diameter < 50 µm), exposure route, mode of application (e.g. spraying aerosol from airplane, fogging/smoke generating) and if used in enclosed spaces.
EU regulations 283/2013 (Annex IV) and 284/2013 mentions that OECD TG 403 'Acute Inhalation Toxicity' and TG 436 'Acute Inhalation Toxicity – Acute Toxic Class Method', are acceptable study guidelines (284/2013, 2013; Commission Regulation (EU) No 283/2013, 2013). The head/nose only exposure shall be used, unless whole body exposure can be justified. For products, consideration shall be given to the possible effects of components on the toxic potential of the total mixture. The biocide regulation states that the Acute Toxic Class Method is the preferred method for the determination of this endpoint.

3.2.4 Skin irritation

These studies shall provide information on the potential for skin irritancy of the active substance and product including, where relevant, the potential reversibility of the effects observed. Before undertaking in vivo studies for corrosion/irritation of the active substance, a weight-of-evidence analysis shall be performed on the existing relevant data. Where insufficient data are available, they can be developed through application of sequential testing. The testing strategy shall follow a tiered approach: (1) the assessment of dermal corrosivity using a validated in vitro test method; (2) the assessment of dermal irritation using a validated in vitro test method (such as human reconstituted skin models); (3) an initial in vivo dermal irritation study using one animal, and where no adverse effects are noted; (4) confirmatory testing using one or two additional animals.

The skin irritancy study of the active substance shall always be provided. Where available, a dermal toxicity study shown not to produce irritation of the skin at the limit test dose level of 2 000 mg/kg body weight shall be used to waive the need for any dermal irritation studies.

EU regulation 283/2013 (Annex IV) lists examples of acceptable study guidelines, e.g. OECD TG 404 'Acute Dermal Irritation/Corrosion', TG 431 'In vitro Skin Corrosion: Human Skin Model Test', TG 430 'In vitro Skin Corrosion: Transcutaneous Electrical Resistance Test', OECD TG 435 'In vitro Membrane Barrier Test Method for Skin Corrosion', and TG 439 'In vitro Skin Irritation: Reconstructed Human Epidermis Test Method' (Commission Regulation (EU) No 283/2013, 2013).

For PPP products consideration shall be given to use the acute dermal toxicity study to provide irritancy information. Findings of severe skin irritation or corrosion in the dermal study may be used instead of performing a specific irritation study. Consideration shall be given to the possible effects of components on the irritant potential of the total mixture. The skin irritancy of the plant protection product must always be determined, except where the co-formulants are not expected to be skin irritant or the micro-organism is shown not to be skin irritant or where it is likely, as indicated in the test guideline, that severe skin effects can be excluded.

3.2.5 Eye irritation

The results of the study shall provide the potential of eye irritancy of the active substance and product including, where relevant, the potential reversibility of the effects observed. Before undertaking in vivo studies for eye corrosion/irritation of the active substance, a weight-of-evidence analysis shall be performed on the existing relevant data. Where available data are considered insufficient, further data may be developed through application of sequential testing. The testing strategy shall follow a tiered approach: (1) the use of an in vitro dermal irritation/corrosion test to predict eye irritation/corrosion; (2) the performance of a validated or accepted in vitro eye irritation study to identify severe eye irritants/corrosives (such as Bovine Corneal Opacity and Permeability (BCOP) assay, Isolated Chicken Eye (ICE) assay, Isolated Rabbit Eye (IRE) assay, Hen's Egg Test - Chorio-Allantoic Membrane assay (HET-CAM)), and where negative results are obtained, the assessment of eye irritation using an in vitro test method for identification of non-irritants or irritants, and where not available; (3) an initial in vivo eye irritation study using one animal, and where no adverse effects are noted; (4) confirmatory testing using one or two additional animals. The eye irritancy of the active substance shall always be tested, except where it is likely that severe effects on the eyes may be produced based on criteria listed in the test methods. EU regulation 283/2013 (Annex IV) lists examples of acceptable study guidelines, e.g. OECD TG 405 'Acute eye irritation/corrosion', TG 437 'Bovine Corneal Opacity and Permeability Test Method for Identifying Ocular Corrosives and Severe Irritants', and TG 438 'Isolated Chicken Eye Test Method for Identifying Ocular Corrosives and Severe Irritants' (Commission Regulation (EU) No 283/2013, 2013).

3.2.6 Skin sensitization

The study shall provide sufficient information to assess the potential of the active substance and product to provoke skin sensitisation reactions. The study shall always be carried out, except where the active substance or co-formulant is a known sensitiser. The local lymph node assay (LLNA) shall be used, including where appropriate the reduced variant of the assay. In case the LLNA cannot be conducted, a justification shall be provided, and the Guinea Pig Maximisation Test shall be performed. Where a guinea pig assay (Maximisation or Buehler), meeting OECD guidelines and providing a clear result, is available, further testing shall not be carried out for animal welfare reasons. Since an active substance identified as a skin sensitiser can potentially induce hypersensitivity reaction, potential respiratory sensitisation should be taken into account when appropriate tests are available or when there are indications of respiratory sensitisation effects. EU regulation 283/2013 (Annex IV) lists examples of acceptable study guidelines, e.g. OECD TG 429 'Skin Sensitisation – Local Lymph Node Assay', TG 406 'Skin sensitization', TG 442A 'Skin Sensitisation – Local Lymph Node Assay: DA', and TG 442B 'Skin Sensitisation – Local Lymph Node Assay: BrdU-ELISA' (Commission Regulation (EU) No 283/2013, 2013).

3.2.7 Phototoxicity

The study shall provide information on the potential of certain active substances to induce cytotoxicity in combination with light, for example active substances that are phototoxic in vivo after systemic exposure and distribution to the skin, as well as active substances that act as photo-irritants after dermal application. The in vitro study shall be required where the active substance absorbs electromagnetic radiation in the range 290-700 nm and is liable to reach the eyes or light-exposed areas of skin, either by direct contact or through systemic distribution. If the ultraviolet/visible molar extinction/absorption coefficient of the active substance is less than 10 L × mol–1 × cm–1, no toxicity testing is required. EU regulation 283/2013 (Annex IV) mentions OECD TG 432 'In vitro 3T3 NRU Phototoxicity Test', and TG 101 'UV-VIS Absorption Spectra', as examples of acceptable study guidelines (Commission Regulation (EU) No 283/2013, 2013).

3.3 Short-term toxicity

Short-term toxicity studies shall be designed to provide information as to the amount of the active substance that can be tolerated without adverse effects under the conditions of the study and to elucidate health hazards occurring at higher dose levels. Studies typically provide information on target organs where relevant (including immune, nervous and endocrine systems); No Observed Adverse Effect Level (NOAEL) thresholds; the time course

and characteristics of adverse effects with full details of behavioral changes and possible pathological findings at post-mortem; where relevant the persistence and reversibility of certain adverse effects observed following discontinuation of dosing; where possible, the mode of toxic action; and, the relative hazard associated with the different routes of exposure. If nervous system, immune system or endocrine system are specific targets in short term studies at dose levels not producing marked toxicity, supplementary studies, including functional testing, shall be carried out. Toxicokinetic data (that is to say blood concentration) shall be included in short term studies. In order to avoid increased animal use, this data may be derived in range finding studies. Short-term studies provide information useful in the design of chronic toxicity studies.

3.3.1 Oral 28 days

28-day studies are not required for active substances in PPPs but shall be reported if available. Examples of study guidelines are OECD TG 407 'Repeated Dose 28-day Oral Toxicity Study in Rodents' (2008) and OECD TG 412 'Subacute Inhalation Toxicity: 28-Day Study' (2018).

3.3.2 Oral 90 days

Oral 90-day studies are required both in rodents, usually the rat, as well as in non-rodents (dogs) for active substances in PPPs. In the 90-day study, potential neurotoxic and immunotoxic effects, genotoxicity by way of micronuclei formation, and effects potentially related to changes in the hormonal system shall be carefully addressed. Histopathology and clinical biochemical examinations are carried out at the end of the study or in case of death. Based on previous knowledge of the chemical or a close analogue, consideration should be given to include additional satellite groups in the control and in the top dose group for observation after the treatment period, for the potential reversibility or persistence of any toxic effects. OECD TG 408 'Repeated dose 90-day oral toxicity study in rodents' (2018) and OECD TG 409 'Repeated Dose 90-Day Oral Toxicity Study in Non-Rodents' (2018) can be suitable.

Also, for active substances in biocidal products, testing also in a second species (non-rodent) may be required depending on study outcomes and circumstances (528/2012).

3.3.3 Other routes, 90 days

For human risk assessment, additional dermal studies shall be considered on a case-by-case basis, unless the active substance is a severe irritant. A suitable study guideline can be OECD TG 411 'Subchronic Derman Toxicity: 90-day Study' in adult rat, rabbit or guinea pig (2019).

For volatile active substances (vapour pressure $>10^{-2}$ Pascal) expert judgement (for example based on route-specific kinetic data) is required to decide whether the short-term studies have to be performed by inhalation exposure. Then, OECD TG 413 'Subchronic Inhalation Toxicity: 90-day Study' in rodents (rats are preferred) can be suitable.

3.3.4 Genotoxicity testing

The purpose of genotoxicity testing for risk assessment of substances in food and feed is:

- to identify substances which could cause heritable damage in humans,
- to predict potential genotoxic carcinogens in cases where carcinogenicity data are not available,
- to contribute to understanding of the mechanism of action of chemical carcinogens

Appropriate dose levels, depending on the test requirements, shall be used in either in vitro or in vivo assays. A tiered (stepwise) approach shall be adopted, with selection of higher tier tests being dependent upon interpretation of results at each stage (EFSA, 2011).

A genotoxicity testing strategy is described in Annex II of Regulation EU 283/2013 (Commission Regulation (EU) No 283/2013, 2013), and suitable OECD TGs (in vitro, in vivo (somatic and germ cells)) are described in Annex IV. In parallel, the EFSA Opinion of 2011 also describes the testing strategy to be followed for food and feed safety assessment. In this EFSA Opinion, a tiered approach is recommended by the Scientific Committee starting with in vitro, and if appropriate, in vivo testing.

For an adequate evaluation of the genotoxic potential of a chemical substance, different endpoints, i.e., induction of gene mutations, structural and numerical chromosomal alterations, need to be assessed.

The Scientific Committee recommends use of the following two in vitro tests as the first step in testing:

- a bacterial reverse mutation test (OECD TG 471), and
- an in vitro mammalian cell micronucleus test (OECD TG 487).

In vivo tests should relate to the genotoxic endpoint(s) identified as positive in vitro and to appropriate target organs or tissues. Evidence, either from the test itself or from other toxicokinetic or repeated dose toxicological studies, that the target tissue(s) have been

exposed to the test substance and/or its metabolites is essential for interpretation of negative results.

The approach to in vivo testing should be stepwise. If the first test is positive, no further test is needed, and the substance should be considered as an in vivo genotoxin. If the test is negative, it may be possible to conclude that the substance is not an in vivo genotoxin. However, in some cases, a second in vivo test may be necessary as there are situations where more than one endpoint in the in vitro tests is positive and an in vivo test on a second endpoint may then be necessary if the first test is negative. It may also be necessary to conduct a further in vivo test on an alternative tissue if, for example, it becomes apparent that the substance did not reach the target tissue in the first test. The combination of assessing different endpoints in different tissues in the same animal in vivo should be considered.

The Scientific Committee (EFSA, 2011) recommends the following as suitable in vivo tests:

- A mammalian erythrocyte micronucleus test (OECD TG 474),
- A transgenic rodent somatic and germ cell gene mutation assays (OECD TG 488)
- An in vivo Comet assay; OECD TG 489(Dirven et al., 2023).

The in vivo micronucleus test covers the endpoints of structural and numerical chromosomal aberrations and is an appropriate follow-up for in vitro clastogens and aneugens. There may be circumstances in which an in vivo mammalian bone marrow chromosome aberration test (OECD TG 475) may be an alternative follow-up test. To follow up on positive *in vitro* results for aneugenicity, for substances that are aneugenic but not clastogenic nor causing gene mutations, EFSA's Scientific Committee states that the preferred approach is to perform an *in vivo* mammalian erythrocyte micronucleus test with a relevant route of administration (EFSA, 2021).

Transgenic rodent assays can detect point mutations and small deletions and are without tissue restrictions. The in vivo Comet assay is considered a useful indicator test in terms of its sensitivity to substances which cause gene mutations and/or structural chromosomal aberrations and can be used with many target tissues.

EFSA's Scientific Committee concluded that routine testing for genotoxicity in germ cells is not necessary. A substance that is concluded to be positive in tests in somatic tissues in vivo would normally be assumed to reach the germ cells and to be a germ cell mutagen, and therefore potentially hazardous to future generations. In the contrary situation, a substance that is negative in tests in somatic tissues in vivo would be assumed to be negative in germ cells, and moreover no germ cell-specific mutagen is known

EFSA's Scientific Committee recommends a documented weight-of-evidence approach to the evaluation and interpretation of genotoxicity data. Such an approach should not only consider

the quality and reliability of the data on genotoxicity itself, but also take into account other relevant data that may be available, such as physico-chemical characteristics, structure-activity relationships (including structural alerts for genotoxicity and „read-across" from structurally related substances), bioavailability, toxicokinetics and metabolism, and the outcomes of any repeated-dose toxicity and carcinogenicity studies.

Special testing requirements in relation to photomutagenicity may be indicated by the structure of a molecule. If the Ultraviolet/visible molar extinction/absorption coefficient of the active substance and its major metabolites is less than 1 000 L × mol–1 × cm–1, photomutagenicity testing is not required; TG 498 (OECD, 2023).

3.4 Long-term toxicity and carcinogenicity

OECD Test Guidelines (TG) 451 (Carcinogenicity Studies) 452 (Chronic Toxicity Studies) and 453 (Combined chronic/carcinogenesis studies) have been updated in 2018. Long-term chronic toxicity is defined as adverse effects occurring after the repeated or continuous administration of a test sample for a major part of the life span, or for all of its lifespan. For rodents, this is usually considered to be six months in duration. The study design and endpoints evaluated are similar to the subchronic toxicity. Repeat dose toxicity studies are usually conducted in animals with the main aim of defining a NOAEL.

The dog has been a commonly used non-rodent species in chronic toxicity studies in the past. In recent years, the 90 days subchronic toxicity dog study is considered sufficient as longer duration is not adding substantial value for regulatory decisions. The use of non-rodent species may be considered when available data suggest that they are more relevant for the prediction of health effects in humans. In such cases, TG 409 with the appropriate modifications should be applied.

Consideration should be given to the selection of exposure route (most commonly oral, but long–term chronic toxicity studies involving exposure via the dermal or inhalation routes may also be necessary) and dose selections (see Guidance Document No. 116), and whether there are combined chronic toxicity and carcinogenicity studies (TG453) or separate execution of a chronic toxicity study (TG 452) and carcinogenicity study (TG 451). Guidance for analysis and evaluation of chronic toxicity and carcinogenicity studies are available (OECD 35/14, 2002).

Combined chronic toxicity/carcinogenicity study (OECD TG 453)

The rat is typically used for such studies. For rodents, each dose group and concurrent control group intended for the carcinogenicity phase of the study should contain at least 50 animals of each sex, while for the chronic toxicity phase of the study should contain at least 10 animals of each sex. At least three dose levels should be used, in addition to the concurrent control

group for both the chronic toxicity phase and the carcinogenicity phase of the study. The three main routes of administration are oral, dermal, and inhalation. The Test Guideline focuses on the oral route of administration. The period of dosing and duration of the study is normally 12 months for the chronic phase, and 24 months for the carcinogenicity phase. The study report should include: measurements (weighing) and regular detailed observations (haematological examination, urinalysis, clinical chemistry), as well as necropsy procedures and histopathology. All these observations permit the detection of neoplastic effects and a determination of carcinogenic potential as well as the general toxicity.

The objectives of the studies covered by TG 453 include:

- The identification of the carcinogenic properties of a chemical, resulting in an increased incidence of neoplasms, increased proportion of malignant neoplasms or a reduction in the time to appearance of neoplasms, compared with concurrent control groups;
- The identification of the time to appearance of neoplasms;
- The identification of the chronic toxicity of the chemical;
- The identification of target organ(s);
- Characterisation of the dose:response relationship,
- Identification of NOAEL or point of departure for establishment of a Benchmark Dose (BMD),
- Extrapolation of carcinogenic effects to low dose human exposure levels,
- Prediction of chronic toxicity effects at human exposure levels,
- Provision of data to test hypotheses regarding mode of action

Prospects for replacing animal use for chronic and repeat dose toxicity testing are, at present, limited and there are no validated alternative repeat-dose/subchronic tests accepted for regulatory testing yet (EURL ECVAM). However, there are many projects and initiatives at the international level which aim to implement various aspects of replacement, reduction and refinement (the 3Rs) in RDT testing. Therefore, some case studies demonstrating the use of Next Generation Risk Assessment applying various new approach methodologies (NAMs) may provide relevant information.

For biocides, see section 3.11 of Regulation 528/2012 (Annex II) for biocidal products (Commission Regulation (EU) No 528/2012, 2012).

3.5 Reproductive toxicity

Possible effects on reproductive physiology and the development of progeny shall be investigated and reported concerning the following aspects:

- Impairment of male and female reproductive functions or capacity (i.e. effects on oestrus cycle, sexual behaviour, any aspect of spermatogenesis or oogenesis, or hormonal activity or physiological response which would interfere with the capacity to fertilise, fertilisation itself or development of the fertilised ovum up to and including implantation).
- Harmful effects on the progeny (i.e. effect interfering with normal development, both before and after birth. This includes morphological malformations such as anogenital distance, nipple retention, and functional disturbances (such as reproductive and neurological effects).
- Effects accentuated over generations shall be reported

OECD TG 421, 422, 443, 414, 416 and 426 were updated in 2018. The guidance document (*Revised Guidance Document 150 on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption*) was also updated in 2018.

Reproduction/Developmental Toxicity Screening Test and Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OECD TG 421 and 422, 2018):

TG 421/422 are OECD validated methods for evaluating effects of a test chemical on male and female reproductive performance. The TG is designed to be used with the rat and has been updated with endocrine disruptor endpoints, in particular measure of anogenital distance and male nipple retention in pups and thyroid examination. Males are dosed for a minimum of four weeks and females should be dosed throughout the study (~ 63 d). At least three test groups and a control group should be used, and each group should be started with >10 animals of each sex. Dose levels may be based on information from acute toxicity tests or on results from repeated dose studies. The test substance is administered orally and daily.

The results of this study include clinical observations, body weight and food/water consumption, oestrous cycle monitoring, offspring parameters observation/measurement, thyroid hormone measurement, as well as gross necropsy and histopathology. The findings of this toxicity study should be evaluated in terms of the observed effects, necropsy and microscopic findings. Because of the short period of treatment of the male, the histopathology of the testis and epididymis should be considered along with the fertility data, when assessing male reproductive effects.

Extended One-Generation Reproductive Toxicity (OECD TG 443, 2018):
TG 443 is designed to provide an evaluation of reproductive and developmental effects that may occur because of pre- and postnatal chemical exposure as well as an evaluation of

systemic toxicity in pregnant and lactating females and young and adult offspring. In the assay, sexually mature male and female rodents (parental (P) generation) are exposed to graduated doses of the test substance starting 2 weeks before mating and continuously through mating, gestation and weaning of their pups (F1 generation). At weaning, pups are selected and assigned to cohorts of animals for reproductive/developmental toxicity testing (cohort 1), developmental neurotoxicity testing (cohort 2) and developmental immunotoxicity testing (cohort 3). The F1 offspring receive further treatment with the test substance from weaning to adulthood. Clinical observations and pathology examinations are performed on all animals for signs of toxicity, with special emphasis on the integrity and performance of the male and female reproductive systems and the health, growth, development and function of the offspring. Part of cohort 1 (cohort 1B) may be extended to include an F2 generation; in this case, procedures for F1 animals will be similar to those for the P animals.

Two-Generation Reproduction Toxicity (OECD TG 416, 2018):

TG 416 is an OECD validated two-generation reproduction test designed to provide general information concerning the effects of a test substance on the integrity and performance of the male and female reproductive systems, and on the growth and development of the offspring. The test substance is administered daily in graduated doses to several groups of males and females. Males and females of the Parent generation (5-9 weeks old) should be dosed during growth, during their mating, during the resulting pregnancies, and through the weaning of their first-generation offspring. The administration of the substance is continued to first generation offspring during their growth into adulthood, mating and production of a second generation (until the weaning). The rat is the preferred species for testing. Each test and control group should contain a sufficient number of animals to yield preferably not less than 20 pregnant females at or near parturition. At least three dose levels and a concurrent control shall be used. It is recommended that the test substance be administered orally (by diet, drinking water or gavage). A limit test may be performed if no effects would be expected at a dose of 1000 mg/kg bw/d.

The results of this study include measurements (weighing, sperm parameters, oestrus cycle parameters and offspring parameters), clinical daily observations, as well as gross necropsy and histopathology. The test should provide a satisfactory estimation of a no-effect level and an understanding of adverse effects on reproduction, parturition, lactation, postnatal development including growth and sexual development.

Prenatal Developmental Toxicity (OECD TG 414, 2018):

TG 414 is an OECD validated developmental toxicity test designed to provide general information concerning the effects of prenatal exposure on the pregnant test animal and on

the developing organism. The test substance is normally administered to pregnant animals at least from implantation to one day prior to the day of scheduled kill, which should be as close as possible to the normal day of delivery. This Test Guideline is intended for use with rodent (rat preferably) and non-rodent (rabbit preferably). Each test and control group should contain a sufficient number of females to result in approximately 20 female animals with implantation sites at necropsy. Three concentrations, at least, should be used. The test substance or vehicle is usually administered orally by intubation. A limit test may be performed if no effects would be expected at a dose of 1000 mg/kg bw/d.

The results of this study include measurements (weighing) and clinical daily observations, each day preferably at the same time. Shortly before caesarean section, the females are killed (one day prior to the expected day of delivery), the uterine contents are examined, and the foetuses are evaluated for soft tissue and skeletal changes. Several endocrine-related measurements in the dams and in the foetuses have been added in 2018. In any study which demonstrates an absence of toxic effects, further investigation to establish absorption and bioavailability of the test substance should be considered.

Neurodevelopmental toxicity (OECD TG 426, 2018):

TG 426 is an OECD validated developmental neurotoxicity study providing information on the effects of repeated exposure to a substance during in utero and early postnatal development. The test substance is administered daily, generally orally, to mated females (rats are preferred) from the time of implantation (GD 6) throughout lactation (PND 21). At least three dose levels and a concurrent control should be used and a total of 20 litters are recommended at each dose level. Dams are tested to assess effects in pregnant and lactating females and may also provide comparative information. Offspring are randomly selected from within litters for neurotoxicity evaluation. All dams and all offspring should be carefully observed at least once daily with respect to their health condition, including morbidity and mortality. The evaluation consists of observations to detect gross neurologic and behavioural abnormalities, and the evaluation of brain weights and neuropathology during postnatal development and adulthood.

The report should include the body weight, the food/water consumption, the detailed clinical observations, the necropsy findings, a detailed description of all behavioural, the number of animals at the start and at the end of the study and the toxic response data by sex and dose level.

Neurodevelopmental in vitro test battery DNT IVB: Currently there is not sufficient evidence that the DNT IVB can replace the use of OECD TG426 and OECD TG443. However, DNT IVB can be used as part of the hazard identification and characterisation.

3.6 Neurotoxicity studies

Note that developmental neurotoxicity studies (DNT) fall under reproductive toxicity section above.

Neurotoxicity studies in rodents shall provide sufficient data to evaluate the potential neurotoxicity of the active substance (neurobehavioural and neuropathological effects) after single and repeated exposure. Such studies shall be performed for active substances with structures that are similar or related to those capable of inducing neurotoxicity, and for active substances which induce specific indications of potential neurotoxicity, neurological signs or neuropathological lesions in toxicity studies at dose levels not associated with marked general toxicity. Performance of such studies shall also be considered for substances with a neurotoxic mode of pesticidal action. Consideration shall be given to include neurotoxicity investigations in routine toxicology studies. OECD TG 424 'Neurotoxicity Study in Rodents' (1997) is relevant in which the duration of exposure can be either 28 days, subchronic (90 days) or chronic (1 year or longer). This neurotoxicity study, when used alone or in combination, provides information that can:
• identify whether the nervous system is permanently or reversibly affected by the chemical tested;
• contribute to the characterization of the nervous system alterations associated with exposure to the chemical, and to understanding the underlying mechanism.
• determine dose-and time-response relationships in order to estimate a NOAEL level.

Delayed polyneuropathy (disease of many (peripheral) nerves) studies (acute and repeated) shall be performed/considered for active substances structurally similar or related to organophosphorous compounds known capable of inducing this effect, see OECD TG 419 'Delayed Neurotoxicity of Organophosphorus Substances: 28-day Repeated Dose Study' (1995) in laying hens.

3.7 Other toxicological studies

This section generally focuses on toxicity studies of metabolites, supplementary information on the active substance as well as endocrine disrupting properties where relevant; Annex II of 283/2013 (Commission Regulation (EU) No 283/2013, 2013).

3.7.1 Endocrine disrupting properties

European Chemical Agency (ECHA) and European Food Safety Authority (EFSA) with the technical support of the Joint Research Centre (JRC), published a guidance document on how to identify substances with endocrine disrupting properties in pesticides and biocides in 2018 (ECHA (European Chemicals Agency) and EFSA (European Food Safety Authority) with the technical support of the Joint Research Centre (JRC) et al., 2018).) This guidance

document describes how to perform hazard identification for endocrine-disrupting properties by following the scientific criteria which are outlined in Commission Delegated Regulation (EU) 2017/2100 and Commission Regulation (EU) 2018/605 for biocidal products and plant protection products, respectively.

The Revised Guidance Document 150 on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption originally published in 2012 and updated in 2018 reflect new and updated OECD test guidelines. The OECD Conceptual Framework lists the OECD TGs and standardized test methods available, under development or proposed, that can be used to evaluate chemicals for endocrine disruption. In addition, background on the standardized test methods used, and guidance for interpreting the outcome of individual tests are included.

3.8 Exposure

3.8.1 Dietary exposure

3.8.1.1 Maximum Residue Limit (MRL)

Currently, the estimation of chronic and acute dietary consumer exposure to pesticide residues regarding the setting of, or renewal of MRLs for active substances in the EU primarily employs an Excel-based spreadsheets calculation model, developed by EFSA (Pesticide Residue Intake Model – PRIMo rev 3). Revision 4 of the model, which will be a new web-based tool is in progress. This new beta online tool introduces a new user interface and various improvements, such as the integration of new consumption data and allows for more detailed exposure output reports.

Submission and retrieval of dossiers for applications in the EU occur via the IUCLID software, an International Uniform Chemical Information Database, to create, store, maintain and exchange data on chemical substances. IUCLID is co-developed by the European Chemicals Agency (ECHA) and the Organization for Economic Co-operation and Development (OECD). EFSA's MRL application manual is an excellent supporting publication with detailed information on requirements for the various applications in the EU.

Relevant guidelines, procedural flowcharts and databases:

- Guidelines for requirements regarding MRL
- Procedure for new active substances as well as amendment of approval conditions under Regulation EC 1107/2009

- Procedure for renewal of approval of active substances under Regulation EU 844/2012
- EUs pesticide database for active susbstancesResults from annual monitoring of pesticide residues in food and feed on the Norwegian market, with a risk assessment in relation to MRLs, is published here at NFSA's website. A summary of annual results from the coordinated monitoring program for all EU and EEA countries are published in EFSA's journal. These monitoring programs and datasets provide the continuous control of food safety and risk of dietary exposure to pesticides and metabolites.

3.8.1.2 Combined/cocktail effects

EFSA has developed a tiered approach for grouping pesticides for the implementation of cumulative risk assessment - to assess the risk posed by exposure to multiple pesticide residues. The general methodology for classifying pesticides into so-called cumulative assessment groups (CAGs) is based on identifying compounds that exhibit similar toxicological properties in a specific organ or system. The established CAGs and NOAELs are used to assess the combined risk of exposure to multiple active pesticides based on common target organ/system and/or mode of action.

EFSA has established a method for cumulative risk assessment of pesticides that have effects on the nervous system, thyroid gland and craniofacial malformation (EFSA, 2019, 2020, 2022).

For pesticides with the same biological mechanism of action (MoA), a combined risk for the whole group can be assessed by dose addition model (adding up the levels of each pesticide found in the food susbstance and multiplying by the potency of the individual pesticides). As a conservative approach, EFSA also use dose addition model for pesticides that have same effects but dissimilar MoA. For pesticides with unknown toxicological mechanisms and effects on different organs, it is more complicated to carry out a combined risk assessment.

In 2022, VKM performed an assessment of analysed fruit and berries containing residues of several pesticides in the same sample using a two-tiered approach (VKM et al., 2022). In the first tier, the effect of the mixture was estimated by adding up the hazard quotient (HQ) for the substances, that is, the ratio of exposure to a chemical and an associated toxicological reference value. In the second tier, VKM assessed the risk of combined effects where the hazard index (HI) exceeds 100 percent in tier 1, for substances that act on the same organ/system – the nervous system, the thyroid gland, or both.

In 2018, the OECD published a comprehensive guidance document for assessing the risks of combined exposure to multiple chemicals (OECD, 2018)

A Monte Carlo risk assessment (MCRA; mcra.rivm.nl) toolkit has been developed with models and data to support cumulative (mixture) pesticide exposure risk assessment.

3.8.2 Non dietary exposure (operator, worker, bystander, resident)

In 2014, EFSA issued a guidance on the assessment of exposure of operators, workers, residents, and bystanders to harmonize the methodology and datasets used in this area of risk assessment of PPPs (EFSA, 2014). Prior to this, the member states employed varying datasets and models. This guidance was updated in 2021 with the adoption of these principles:

- The routine risk assessment for individual PPPs should continue to use deterministic methods, and a tiered approach to exposure assessment remains appropriate.
- An acute risk assessment for operators, workers and bystanders should be introduced when PPPs are acutely toxic.
- For acute risk assessments, exposure estimates should normally be based on 95th percentiles of relevant datasets, whereas, for longer term risk assessments, the starting point should be a 75th percentile.

The updated guidance includes a revised user-friendly online calculator that covers new scenarios, updated default values, revised crop groupings, and improved functionalities such as exposure estimates for several active substances in a product, calculation of safe re-entry interval and generation of a report. Recommendations for the design, conduct and interpretation of higher tier field studies have also been provided in the updated guidance. For scenarios that are not covered by these standardised methods, the risk assessor will need to follow an ad hoc approach that is judged to be the most appropriate. An ad hoc, higher tier, exposure assessment may also be used for exposure scenarios that are covered by a standardised first-tier method (EFSA et al., 2022).

3.9 Biocides

Regulation 528/2012 (Annex II) for biocidal products states that testing of active substances shall be performed according to the methods described in regulation 440/2008 for REACH, and that biocidal products are classified, packaged, and labelled in accordance with the approved summary of biocidal products characteristics (528/2012, Article 69). If a method is inappropriate or not described, other methods shall be used which are scientifically appropriate. New tests involving vertebrates shall be conducted as the last available option to comply with the data requirements (528/2012, Annex II). For biocides, non-animal approaches such as use of existing data, weight-of-evidence (WoE) approaches, in vitro

methods, grouping, read-across (e.g. using QSAR) can be used (ECHA, 2017; REACH Regulation Article 13(1)). Annexes II of biocidal product regulations 528/2012 and 2021/525 also specifies study requirements (e.g. that ADME/TK studies are required) and assessments; e.g. of endocrine disruption (Commission Delegated Regulation (EU) 2021/525, 2020; Commission Regulation (EU) No 528/2012, 2012).

3.10 Medical data

Practical data and information relevant to the recognition of the symptoms of poisoning and on the effectiveness of first aid and therapeutic measures shall be submitted.

Data and information relevant to the effects of human exposure, where available, shall be used to confirm the validity of extrapolations made and conclusions reached with respect to target organs, dose-response relationships, and the reversibility of adverse effects. Such data may be generated following accidental, occupational exposure or incidents of intentional self-poisoning, and shall be reported if available.

Reports of occupational health surveillance programs and of monitoring studies shall be submitted. These reports shall, where available, include data from persons exposed in manufacturing plants, or during or after application of the active substance (for example from monitoring studies in operators, workers, residents, bystanders or victims of accidents).

Where available, reports from studies with humans, such as tests on toxicokinetics and metabolism, or tests on skin irritation or skin sensitisation, shall be submitted.

In general, the reference values shall be based on animal studies, but if appropriate scientifically valid and ethically generated human data are available and show that humans are more sensitive and lead to lower regulatory limit values, these data shall take precedence over animal data. Documentation shall be used to confirm the validity of extrapolations from animal data to man and to identify unexpected adverse effects which are specific to humans.

3.11 Alternative methods

For some endpoints, e.g. skin and eye irritation, validated in vitro OECD TGs exist and can be used to replace or reduce animal testing. There is an ongoing development of NAMs employing e.g. cell culture (in vitro) testing. For several endpoints (e.g. reproduction toxicology, carcinogenesis) however, no (or few) NAMs are presently accepted for regulatory testing (Stucki et al., 2022). Most NAMs are not validated, however, adhering to OECD quality guidances (e.g. Good In Vitro method Practices (GIVIMP), or the (Q)SAR Assessment

Framework) can increase data credibility. For mutual acceptance of data (MAD) within OECD, test methods need to first be validated; the three MAD criteria are: 1. The study must have been conducted according to OECD Test Guideines and OECD Principles of GLP; 2. The study must have been conducted in a test facility which has been inspected by a national GLP compliance monitoring programme and; 3. The national GLP compliance monitoring programme must have undergone a successful evaluation by OECD. If all three criteria are met, all OECD member countries as well as adherents to MAD must accept the study data (OECD, 2024).

EURL ECVAM, the European Union Reference Laboratory for Alternatives to Animal Testing, has its mandate and activities outlined in Directive 2010/63/EC on the protection of animals used for scientific purposes and is actively searching for test methods which replace, reduce or refine (the 'Three Rs') the use of laboratory animals in the test process. Methods developed by research laboratories are submitted to EURL ECVAM whose assessment of the robustness, reliability and predictive capacity of the methods is based on independent peer review of validation study reports. The EURL ECVAM library of reference chemicals is a catalogue of chemical lists that can be used to standardize, qualify, characterize or compare in vitro, in chimico and in silico methods and models. It contains chemical lists used in research and validation projects, proficiency chemicals from OECD test guidelines, and chemicals that have been classified within various regulatory contexts (e.g. pesticides, carcinogenic and endocrine disrupters). Link to library: Joint Research Centre Data Catalogue - EURL ECVAM library of reference chemicals - European Commission (europa.eu).

To avoid animal testing, data can sometimes be transferred from one or several structurally similar substances using read-across which is often supported by quantitative structure activity relationship (QSAR) in silico property/toxicity prediction. For relevant impurities in biocides lacking toxicity study data, derivation of threshold of toxicological concern (TTC) values using in silico toxicity predictions (e.g. QSAR) is possible (ECHA, 2020).

3.12 Probabilistic risk assessment

Probabilistic risk assessment (ProbRA) is a group of techniques that incorporate variability, uncertainty and randomness into the risk assessment process. It provides estimates of the range and likelihood of a hazard, exposure or risk, rather than a single point estimate (EPA, 2014). ProbRA can include several techniques such as probability of exposure modeling, PBPK modeling of tissue concentrations, in vitro and in vivo data, IVIVE, QSAR, AOPs, and AI (Maertens et al., 2022). Traditionally, risk assessment has been performed using uncertainty / assessment factors and worst-case / precautionary approaches and thresholds. ProbRA, on the other hand, is fueled by probability of exposure and probability of hazard and susceptibility (Maertens et al., 2022). ProbRA is used for Monte Carlo Risk Assessment

through an EFSA collaboration with RIVM, the Netherlands. The MCRA tool (https://mcra.rivm.nl) includes models for calculating the exposure to pesticides probabilistically. The result of a probabilistic calculation is an exposure distribution, describing the range of exposure levels within a population. There is a difference between probabilistic modelling (most appropriate for exposure for one day), and usual intake modelling (intake for life long period). Acute toxicity of chemicals is for one day, chronic toxicity is based on usual intake. Both situations are covered in the MCRA tool. ProbRA is presently not often used in regulatory risk assessment. ProbRA of hazard remains a challenge, e.g. since cell lines (in vitro testing) are often derived from just one individual. In practice, it is still deterministic risk assesssment (the output of the model is fully determined by the parameter values and the initial values) that is used for pesticides in Europe.

3.13 Benchmark-dose (BMD)

EFSA guidance document on the use of the benchmark dose approach in risk assessment was updated and published in 2022 (EFSA Scientific Committee et al., 2022). The benchmark dose (BMD) approach is a more advanced method compared to NOAEL approach for deriving a Reference Point (RP)/ Point of departure (POD) (i.e., toxicity dose that can be used as a starting point for risk assessment). BMD is a dose level, estimated from the fitted dose–response curve, associated with a specified change in response (e.g., 10%) relative to the control group (background response), the benchmark response (BMR). The BMDL is the lower bound of the BMD's credible (confidence) interval, and this value is normally used as the POD. The BMD approach is applicable to all toxicological effects and makes use of all the dose–response data to estimate the shape of the overall dose–response relationship for a particular endpoint. The advantage of the BMD approach over the NOAEL approach:

- POD takes into account the complete set of BMD credible (confidence) intervals for the endpoints considered.
- combines the information on uncertainties in the data, whereas in the NOAEL approach, experimental uncertainties resulting from, e.g., low study power, are not adequately covered and may result in a POD that is significantly higher than the actual POD.
- provides a formal quantitative evaluation of data quality, also considering all aspects of the specific data.

EFSA's recommendations for future risk assessments are to use BMD instead of NOAEL. However, NOAELs might be more easily available, even though there are limitations in the comparison (based on different study types, different species and dependent on dose selection).

Use of the NOAEL is still the standard procedure for derivation of a regulatory limit in many cases, including the US Environmental Protection Agency (U.S. EPA, 2024) and the OECD

Guidelines for the Testing of Chemicals (OECD, 2018); for example the evaluation of neurotoxicity in rodents, OECD, 424 (ECHA, 2017; OECD, 2018; Pouzou et al., 2020).

4 Environmental exposure

4.1 Environmental fate and behaviour

An assessment of the pesticide's fate in the environment is central to the full assessment of the potential environmental risk. The fate in the environment is described by where and in what concentrations pesticides occur in the natural environment/different environmental compartments after their intended use. Some pesticides degrade quickly in the environment and may only cause a short and local impact in the sprayed field, while others may have a strong sorption (binding) to soil particles which, combined with a slow degradation, will lead to an accumulation in the soil after repeated use. Still others may tend to be transported from the soil and primarily affect recipient water bodies. In a field situation, a substance will disappear from the sprayed area due to evaporation, drift, leaching, runoff, abiotic degradation (photolysis, hydrolysis) and biodegradation (see Figure 4.1) as well as by plant uptake.

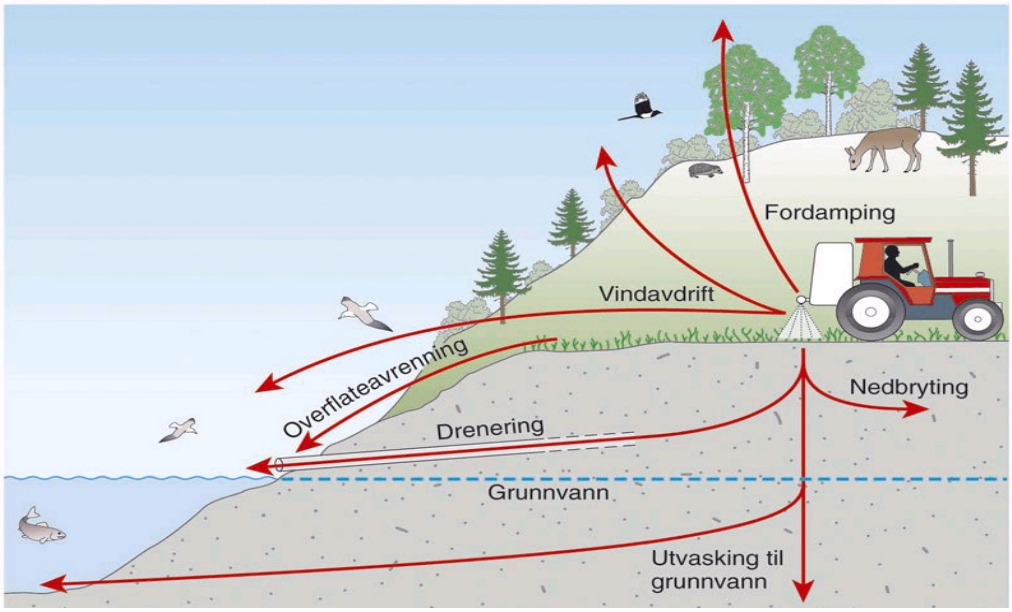

Figure 4.1: Different routes of transport of pesticides from the sprayed field to different environmental compartments. Source: (Mattilsynet og Bioforsk Plantehelse, 2012).

An active substance, safener or synergist shall only be approved where it is not considered to be a:

- Persistent organic pollutant (POP), meaning specific criteria for persistence, bioaccumulation and potential for long-range transport must be fulfilled; cf. Regulation 1107/2009, section 3.7.1 (Commission Regulation (EC) No 1107/2009, 2009).
- Persistent, bioaccumulative and toxic (PBT) substance), meaning specific criteria for persistence, bioaccumulation and toxicity must be fulfilled; cf. Regulation 1107/2009, section 3.7.2 (Commission Regulation (EC) No 1107/2009, 2009).
- Very persistent and very bioaccumulative substance (vPvB), meaning specific criteria for persistence and bioaccumulation must be fulfilled; cf. Regulation 1107/2009, section 3.7.3 (Commission Regulation (EC) No 1107/2009, 2009).

Further, to safeguard groundwater, the predicted concentration of the active substance or of metabolites, degradation or reaction products in groundwater must be shown, for a selection of relevant cases, to comply with the respective criteria of the uniform principles for evaluation and authorisation of plant protection products; cf. Regulation 1107/2009, Article 29(6) (Commission Regulation (EC) No 1107/2009, 2009).

In the EU, ecotoxicological risk/exposure assessment takes place according to a step-by-step procedure and a distinction between "first tier" and "higher tier". The idea of a step-by-step procedure is that one starts with a simple "conservative" assessment and only moves on if necessary. In this context, conservative means being on the safe side in relation to a risk assessment, and therefore based on worst-case calculations. If negligible risk is documented already in step 1 ("first tier"), the substance is considered safe to use. In cases where, as a result of risk calculations, areas of risk are identified according to given acceptance criteria, modifications are made to the underlying assumptions (for example in relation to exposure), so that the risk calculations are more realistic. An assessment of the relevance of foreign studies to Norwegian conditions (e.g. climatic) is often central to this. An example of this concept is given in Figure 4.1.2.3.

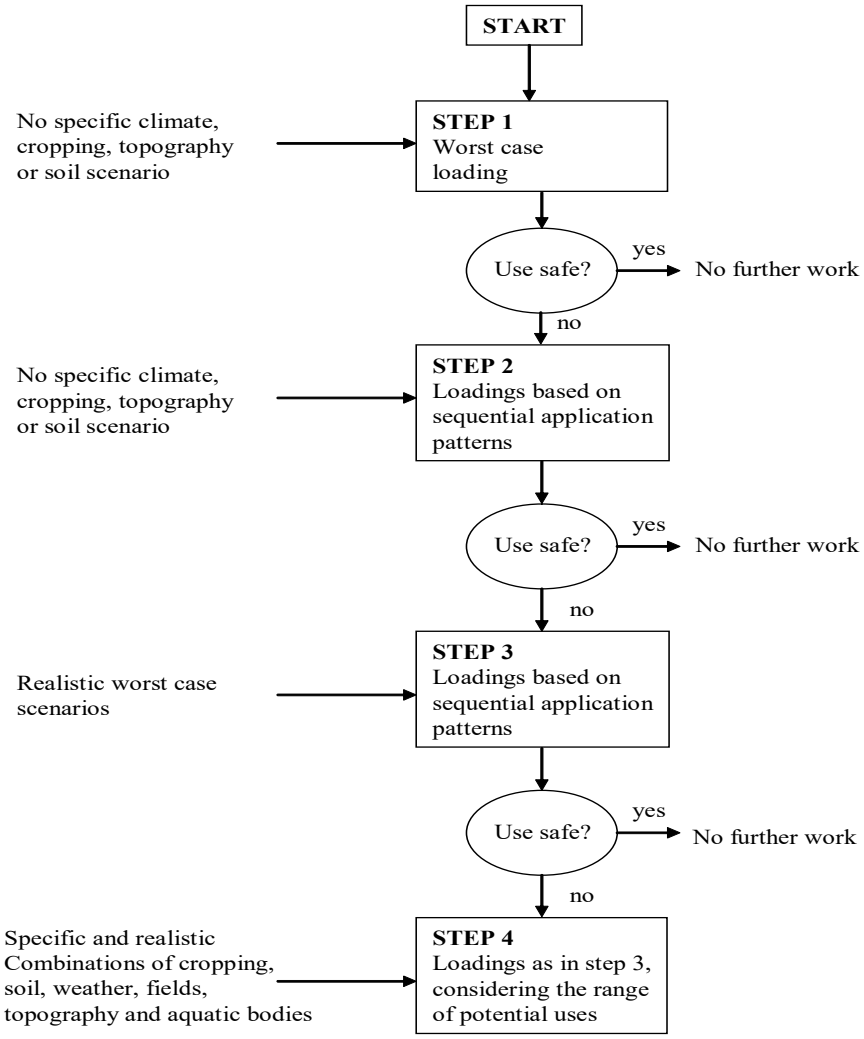

Figure 4.1.2.2: Procedure for a step-by-step exposure assessment of pesticide residues in surface waters in the EU.

4.1.1 Physical/chemical properties

How a pesticide behaves in the environment depends on physical chemical properties of the pesticide (water solubility, vapor pressure, binding to particles, charge and potential for bioconcentration in organisms) and the environment (soil, water, air, other substances). How the pesticide residues, interacts and/or moves through, as well as chemical stability and biodegradability.

How the pesticide's physical chemical properties are assessed in risk assessments is set out in the EU Uniform Principles ((EU) No 546/2011) – see link: https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:155:0127:0175:EN:PDF). Some substances form stable metabolites that may also be relevant in assessing environmental risk.

4.1.2 Fate and behaviour in (unsaturated) soil

Persistence - is one of the most important parameters by which the fate of a pesticide is assessed. An active substance, safener or synergist fulfils the persistence criterion where there is evidence that the time it takes for a degradation of 50% (DT50) in water is greater than 2 months, or that its DT50 in soil is greater than 6 months, or that its DT50 in sediment is greater than 6 months.

The mobility of a substance is another very important parameter in the assessment of a pesticide behaviour. Mobility is assessed from case specific studies in soil where the substance's ability to bind to, among other things, soil particles (adsorption / sorption) is investigated. Data from mobility / sorption studies can be used to estimate transport of pesticides and can be used to calculate the predicted environmental concentration of a substance (PEC).

4.1.2.1 Rate of degradation in soil

Degradation is primarily assessed on the basis of experiments in soil and water/sediment. The rate of degradation is given as the half-life of the compound; the time-period until the concentration of the pesticide is halved (DT50). Both laboratory studies and field studies are used to estimate degradation under different conditions. The strength of studies conducted in the laboratory is that they are conducted under controlled comparable experimental conditions. Field trials have been carried out under more realistic conditions and will be influenced by factors related to local soil and climate conditions.

Among the laboratory studies used to assess degradation rate, DT50 and DT90 (time before 50 and 90% of the substance are degraded respectively) must be estimated/calculated from experiments with at least 4 soil types with different properties. The soil types used must all be relevant to what is "normal" for an agricultural soil. This means that the pH should be between 5.5–7 (pay special attention to weak acids) and organic carbon (OC) should be in the range of 1.5–3%.

The extent to which a substance decomposes depends on factors such as soil type and climate. A substance can thus have different half-lives in different places and there is therefore room for expert assessment in the choice of which degradation values one can choose to use from, for example, field studies.

Current guidance documents to assess persistence and degradation kinetics, as outlined in the Guidance document on work-sharing in the northern zone (Northern Zone 2023), include the following:

- Generic Guidance for Estimating Persistence and Degradation Kinetics from Environmental Fate Studies in Pesticides in EU Registration (version 1.1, 18 December 2014): Based on the official guidance document of FOCUS Degradation Kinetics in the context of 91/414/EEC and Regulation (EC) No 1107/2009, SANCO/10058/2005 version 2.0 (final). June 2006.
- EFSA Journal 2014; 12(5):3662. EFSA Guidance Document for evaluating laboratory and field dissipation studies to obtain DegT50 values of active substances of plant protection products and transformation products of these active substances in soil

The specific test guidelines and requirements for types of studies are detailed in Annex to Regulation (EU) No 283/2013 and 284/2014 on data requirements for active substances and plant protection products, respectively.

4.1.2.2 Adsorption, desorption, and mobility in soil (unsaturated zone)

Mobility is assessed from case specific studies in soil where the substance's ability to bind to, among other things, soil particles (adsorption / sorption) is investigated. This may be sorption studies, column studies or lysimeter studies (see under definitions and terms for further explanation of column and lysimeter studies). Data from such mobility / sorption studies can be used in computer models that estimate the transport of pesticides, either vertically to groundwater, or horizontally to surface water, and can be used to calculate the predicted environmental concentration of a substance (PEC).

A substance that binds strongly to particles is less likely to be transported through the soil than a substance that binds weakly. It is often the case that the more water-soluble a

substance is, the more mobile it is. On the other hand, there is a greater risk that substances that bind strongly to particles are transported by surface runoff over land (4.1.4.3) and by macropore transport through the soil. The soil's content of organic carbon and clay can have an influence on the degree of bonding. Many substances bind either to clay or to organic matter. PH may also have an impact on the binding of certain groups of substances.

In recent years, more emphasis is put on the risk/process of aged sorption. The current guideline for handling this as part of the core assessment in the Northern Zone (Northern Zone 2023) include:

- Guidance on how aged sorption studies for pesticides should be conducted, analysed and used in regulatory assessments, SANTE/12586/2020 – REV 0 (26 January 2021). *The Northern Zone would accept aged sorption endpoints if they are agreed at EU level, however the Northern zone can assess, on a case by case basis, whether or not to use aged sorption refinements for groundwater modelling.*

Pesticides are transported through the environment in different ways. It is important to estimate how much of a pesticide reaches places other than where they are thought to work.

Exposure calculations in the form of model simulations are performed in accordance with guidelines from the FOCUS (FOrum for the Co-ordination of pesticide fate models and their USe) group (link). The FOCUS group was established by the European Commission to harmonize calculations of pesticide concentrations in the environment. However, it is important to point out that all models are simplifications of reality with the risk of systematic errors and artifacts (illegitimate or false observation/result) that this entails. The FOCUS group writes that a lot of work has been done to reduce uncertainty as much as possible (FOCUS, 2002) with the help of the following measures:

- Selection of soil types, weather data and parameterisation of the models have been put together so that this is as realistic and representative as possible for regions in the EU, while at the same time, since it is the "first tier", must be "worst case"
- Independent quality checks of scenario files and model skins have been performed.
- All scenarios are simulated with sample material with different properties.

The FOCUS scenarios represent locations with given properties (temperature, soil, precipitation) that are to a greater or lesser extent relevant to Norwegian conditions. The FOCUS scenarios are well documented and widely used in pesticide risk assessments.

4.1.2.3 Predicted environmental concentration of a substance in soil - PEC-soil calculations

In general, degradation (and dissipation) is affected by factors such as temperature, soil type, soil water saturation, and degree of exposure to sunlight. However, the models used to calculate PEC in soil are based on only a few of these processes and will always be a simplification in the conservative direction. The models do not take in photolysis, evaporation or leaching. Current guidance on predicting environmental concentrations of active substances of plant protection products and transformation products of these in soil (2017) outline the recommended and obligatory model tools for such calculations.

The Northern zone collaboration for PPP approval require that the Nordic PECsoil calculator shall be used for the Northern Zone (Northern Zone 2023). DT50 values used for the calculations should be selected by use of the following guidance:

- EFSA Guidance Document for evaluating laboratory and field dissipation studies to obtain DegT50 values of active substances of plant protection products and transformation products of these active substances in soil. EFSA Journal 2014;12(5):3662.

In the calculation of initial soil concentration in the spraying field (PIECsoil) after a single treatment with a pesticide, three factors are central: the half-life of the substance (DT50), dosage and degree of plant cover (from bare ground to 100% plant cover). The degree of plant cover varies depending on the culture and growth stages in which is sprayed.

PECsoil calculations should be based on a "worst case" and "best fit" value from laboratory studies regardless of model (e.g. SFO or FOMC). In this case, "worst case" means the highest DT50 value from laboratory or field studies conducted under conditions relevant to Norway. By "best fit" is meant that the DT50 value used is located on the degradation curve that statistically describes the degradation data in the best possible way. Where relevant, PIEC, PEC after the last treatment and the time-weighted average (PECTWA) are calculated as a basis for the risk assessment.

For substances that decompose slowly, modelling of any accumulation in soil after repeated use will also be carried out as described below, and an associated plateau concentration will be used to assess long-term effects.

By use of the Nordic PEC soil calculator you can extract curves that describe the development of the concentration in soil when spraying over several years. From this curve, one can determine the plateau concentration and the level of accumulation. The model is based on first-order kinetics and also takes into account the temperature curve in the Finnish FOCUS scenario Jokioinen.

The plateau concentration is the "background level" that is established after spraying over several years. The accumulation of the substance stabilizes in the soil and a plateau

concentration is reached. This means that all new material you add is degraded between each season.

While the Northern Zone collaboration have decided to use the Nordic PECsoil calculator, PERSAM ((Persistence in Soil Analytical Model) (VITO NV, 2022) is a software tool for predicting environmental concentrations of plant protection products (PPPs) in soil commissioned by EFSA. This tool was launched in 2013 and later updated in accordance with the EFSA Guidance Document for predicting environmental concentrations of PPPs in soil (EFSA, 2017). It is used to assess the fate of pesticides in soil, and predict the concentration of a pesticide in soil and soil water at different soil depths, immediately after spraying and at different time points after application. A plateau concentration can be estimated and the probability of accumulation be assessed when use of a pesticide/substance over time. Model scenarios have been developed for all three regulatory zones within the EU. The performance of the PERSAM tool for Norwegian conditions have not been assessed,

Recent mapping and monitoring studies of pesticides in European soils reveal a, possibly, larger occurrence of pesticide residues than anticipated (e.g. (Silva et al., 2019) Silva et al. 2019). LUCAS Soil Pesticides is a European wide soil monitoring survey (Orgiazzi et al., 2022), with a Norwegian pesticide sub-program being established during 2023-2024 as part of a Norwegian Agricultural Soil Monitoring Programme (JordVAAK, 2024; NIBIO, 2024). A recent mapping of pesticide residues in soil in a range of Norwegian soils, climate and cropping conditions (Lang et al., 2023) give an indication of the situation for Norwegian agricultural soils in relation to the European results reported through LUCAS so far.

4.1.3 Fate and behaviour in water

4.1.3.1 Risk of runoff to surface water and groundwater

For surface water, the EU states in Uniform principles that a pesticide should not be approved if:

- The limit value (0.1 µg/l) for drinking water will be exceeded in normal use if the surface water is a potential source of drinking water.
- If one can expect the concentration in the water to exceed the effect concentrations for aquatic organisms.

Unless it can be scientifically documented that this will not happen under field conditions relevant to the pesticide's application.

For groundwater, the EU criteria for the approval of pesticides ("Uniform principles" EU 546/2011) state that a pesticide shall not be approved if:

- The limit value (0.1 µg/l) for drinking water will be exceeded in normal use
- If one can expect the concentration in groundwater to exceed 1/10 of the ADI value.

Unless it can be scientifically documented that this will not happen under field conditions relevant to pesticides application.

In principle, the risk of runoff can be assessed in two ways:

- Based on information about concentrations from model simulations, measured values from field experiments, or monitoring data.
- Based on simple models with key parameters or matrices of key parameters (such as sorption and decomposition) assessed in relation to factors such as climate, soil and spraying practices.

4.1.3.2 Surface water (PEC sw)

There are three main transport routes to surface water; drift, surface runoff and runoff via drainage pipes (see Figure 1). Drift in different crops can be calculated according to Rautmann et al., 2001, but also surface runoff models as described below can be used to estimate drift. If the simulation model uses high concentrations in water immediately after spraying, this will be due to spray drift.

In the EU approval process, surface water is divided into two different types of scenarios, surface runoff and drainage. The EU follows the procedure previously outlined in the report in Chapter 2.4 p. 34 (SANCO/4802/2001) when assessing surface water PEC. Step (STEP) 1 should provide conservative calculation of PEC, i.e. the calculations are made with a good margin of safety and with the most adverse conditions ("worst case"). STEPS 1 and 2 do not take into account climate or soil types, while STEP 3 takes into account climate, soil, slope, etc. Calculations can be made for both active substances and metabolites.

Input values needed in the relevant data models are: molecular weight, water solubility, $DegT50_{soil}$, Koc, $DegT50_{watered/sediment}$, number of sprayings, type of cultures (low cultures, berries and fruits) and the period between sprayings. Degradation studies representative of surface water are conducted using standardized two-phase tests (water and sediment) and half-lives from these studies are used in the models.

In addition to the PIEC and PEC_{twa} values, the $PEC_{global\ maximum}$ is calculated using the FOCUS tool. The PEC_{global} maximum is the maximum concentration from the surface water simulations. This type of PEC value is widely used in risk calculations for effects on aquatic organisms (chapter 3.2).

Evaluation of modelling results using the EU FOCUS scenarios should be made with reference to the recent evaluation of the representativeness of the EU FOCUS scenarios in comparison with Norwegian surface runoff scenarios (VKM Report 2021: 11). Based on this report and their own evaluation, the Norwegian Food Safety Authority has from November 2023 reduced the required number of model scenarios for surface runoff from 9 to 6. See details in; (Mattilsynet, 2023). The details pertaining this will be incorporated in the Northern Zone Guidance Document during 2024. These new requirements do not include any national Norwegian scenarios.

In STEP 4, higher tier assumptions are made to make the simulations even more realistic. The effect of various risk-reducing measures and how to take this into account in the model simulations is assessed in FOCUS (2007). The Northern Zone (2023) includes/allows the use of non-spray buffer zones to mitigate drift, runoff vegetative buffer zone, and drift reducing nozzles in selected cases. It is important to point out that in the EU context there is no agreement on how these calculations should be made. This applies in particular to the importance of vegetation zones and buffer zones on runoff. In the EU Draft Assessment Report (UK, 2010) and Addendum to DAR (UK, 2012), an assumption has been used that pesticide concentrations after surface runoff are reduced by 80 % in the 20-metre spray-free zone. In a meeting in May 2012, VKM considered this assumption not to be well enough justified science to be representative of Norwegian conditions, especially in relation to the fact that Norwegian fields can be quite a bit steeper than many other places in Europe. Recent research studies in Norwegian conditions and sloping areas indicate that a large amount of the surface runoff might infiltrate in the buffer zone and be transported through the soil to macropores and drainage pipes, hence reducing the effectiveness of a buffer strip or spray free zone with regard to retaining pesticides from surface runoff (Holten et al., 2024).

In Norway, we have our own monitoring program, JOVA, which has been going on for many years (ca. 1995 onwards) and provides an important data source for measured environmental exposure concentrations in agricultural streams. For a more detailed description of the JOVA programme and access to reported results, see https://www.nibio.no/jova.

4.1.3.3 Groundwater (PECgw)

In all applications for approval of pesticides for outdoor use, manufacturers perform calculations of pesticide concentrations (PEC values) in groundwater using modelling tools prepared by the FOCUS group for groundwater (FOCUS, 2009). For practical reasons, FOCUS has decided to use simulated concentrations at a depth of 1 m as a realistic "worst case"

with regard to leaching to groundwater (step 1) and if these simulations give concentrations > 0.1 µg/L, a further and stepwise ("higher tier") assessment must be made (FOCUS 2009).

According to the Northern Zone (2023) the following guidance is to be used for the core assessment of groundwater:

- SANCO/321/2000 rev.2. November 2000. FOCUS groundwater scenarios in the EU review of active substances.
- Generic Guidance for Tier 1 FOCUS Ground Water Assessments (version 2.2, May 2014): Based on the reports of the FOCUS Groundwater Scenarios workgroup (finalised in 2000), the FOCUS Ground Water Work Group (as noted in 2014) and the FOCUS Work Group on Degradation Kinetics (finalised in 2009) as modified by EFSA DegT50 guidance (as noted in 2014). *Please note that no member states in the Northern Zone accept non-equilibrium sorption in the modelling approach*.

The 0.1 µg/L limit value for drinking water also applies to relevant metabolites of pesticides.

Relevant metabolites refer to pesticide degradation products that can be assumed to have comparable biological activity with the parent substance or that have specific toxicological properties that are undesirable and harmful.

Various input parameters are used in these models:

- Degradation/DT50 in soil. Soil type often has a great influence on the rate of degradation of substances in soil. There are specific requirements for degradation parameters that are used as input for calculating groundwater concentrations.
- The degree of binding/sorption. The degree of binding to soil particles depends both on substance properties (e.g. charge, fat solubility) and on soil properties.
- Dosage and time of application. The model simulations supplied by the manufacturer should reflect the dose that is planned to be used in the Norway. Experience shows that there is not always the same spraying time and not the same development of plant cover in Norway as further south in Europe, so this should be taken into account.

To represent different field situations in the calculation of concentrations in groundwater, a selection of combinations of soil types, temperature, and precipitation regimes are used in simulations. For groundwater, there are nine different locations in both northern and southern Europe where climate data and soil types are combined into scenarios. There are four simulation models that are used and can be downloaded from FOCUS's website. PRZM (version 3.20), PEARL (version FOCUSPearl_4.4.4), PELMO (version 3.2), and MACRO (version 4.3). The simulations are actively used in assessing whether the concentration of the individual pesticide can exceed 0.1 µg/L, which is the limit value for pesticides in drinking

water. Norwegian groundwater scenarios have been developed (VKM, 2015) as part of the higher tier assessment but is not used in the approval process.

The validity range of the models is limited to neutral organic substances, and the soil profile in the different scenarios is homogeneous (equally structured in all layers). Substances that have a pH-dependent charge and behavior will not be well looked after in such models. Models are simplifications of a complex reality and will never quantitatively reflect the processes a pesticide undergoes in nature. However, we use models because they can show how changes in a combination of local and substance-given parameters are expected to affect, for example, the amount of a substance leaking into water. The panel on plant protection products is aware of the limitations inherent in both models and the scenarios for which simulations are performed and will discuss the relevance of estimated exposure concentrations both in relation to the properties of the substance and the relevance of different scenarios for Norwegian conditions. In this context, considerable emphasis will also be placed on Norwegian monitoring data. These are actual field data that represent a source for validation and reality check on the model performance. Monitoring of groundwater in agricultural dominated areas in Norway is done to some extent (e.g, (Roseth et al., 2022). The results from this monitoring show that pesticides are found in groundwater, usually in low concentrations. Nevertheless, the drinking water limit of 0.1 µg/l has in some cases been exceeded.

When tier 1 assessment does not produce satisfactory results regarding what is considered acceptable groundwater concentrations, FOCUS (2009) further specify tier 2 assessments consists of more refined modelling approaches; tier 2a including more refined parameters, tier 2b including more refined scenarios. Tier 3 consists of four options consisting of different modelling approaches and modelling combined with experiments. Further, a tier 4 is defined to consist of groundwater monitoring data and considered the highest tier of assessment.

Recent scientific evaluations made by the SETAC EMAG-Pest GW, a group of regulatory, academic, and industry scientists, have outlined a framework for groundwater monitoring as a highest tier assessment criterion (Gimsing et al., 2019). These recommendations are however, so far not implemented in current regulations and guidelines. The EFSA PPR Panel reviewed these recommendations and their statement adopted in 2023 (EFSA PPR Panel et al., 2023) concludes that:

…this paper provides many recommendations; however, specific guidance on how to design, conduct and evaluate groundwater monitoring studies for regulatory purposes is missing. The Panel notes that there is no agreed specific protection goal (SPG) at EU level. Also, the SPG has not yet been operationalised in an agreed exposure assessment goal (ExAG). The ExAG describes which groundwater needs to be protected, where and when.

Because the design and interpretation of monitoring studies depends on the ExAG, development of harmonised guidance is not yet possible. The development of an agreed ExAG must therefore be given priority. …

4.1.4 Impact of drinking water treatment processes

The EFSA and ECHA Guidance document on the impact of water treatment processes on residues of active substances or their metabolites in water abstracted for the production of drinking water, ECHA and EFSA et al. (2023) outlines a tiered framework (see figure 4.1.4) for risk assessors and facilitates risk managers in making decisions concerning the approval of active substances (AS) that are chemicals in plant protection products (PPPs) and biocidal products, and authorization of the products. The tiered framework determines whether residues from PPP use or residues from biocidal product use can be present in water at water abstraction locations. Approaches, including experimental methods, are described that can be used to assess whether harmful transformation products (TPs) may form during water treatment and, if so, how to assess the impact of exposure to these water treatment TPs (tTPs) and other residues including environmental TPs (eTPs) on human and domesticated animal health through the consumption of TPs via drinking water. Whenever possible, the framework promotes alternative methods to vertebrate testing, integrating a weight-of-evidence approach.

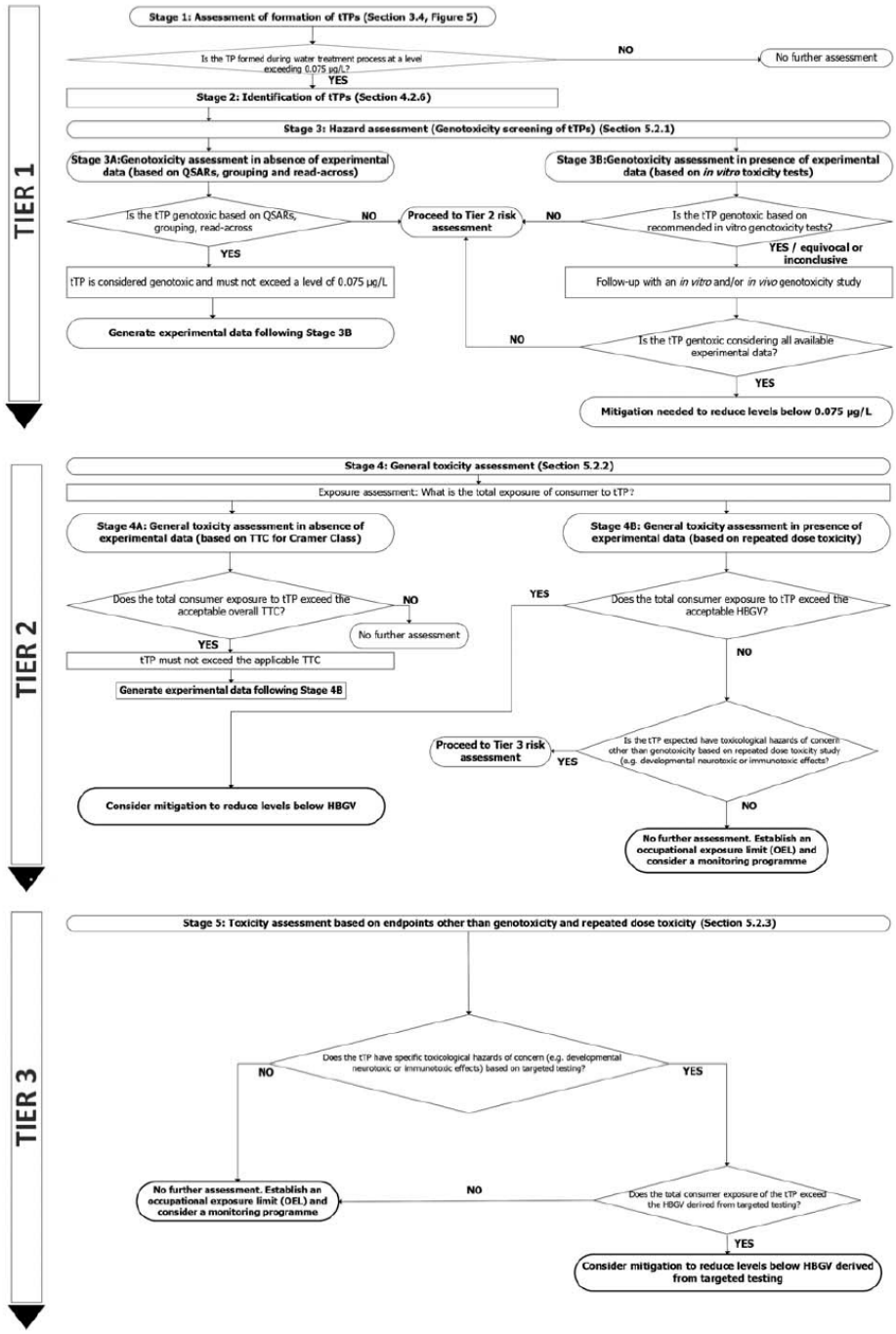

Figure 4.1.4. Flowchart decision scheme for the tiered risk assessment of tTPs of biocides and PPPs formed in drinking water treatment processes in relation to human health or food-producing domesticated animals; a similar decision scheme can be prepared based on Appendix F. In Tier 2, stage 4B: If in vivo general toxicity data are not suitable to set a health-based guideline value (HBGV), proceed to Tier 3 risk assessment (ECHA and EFSA et al., 2023).

4.1.5 Fate in wastewater treatment plants

There are no guidance documents from EFSA or ECHA on the assessment of the fate of pesticides in wastewater treatment plants (WWTPs). However, the SimpleTreat model, developed by the Dutch National Institute of Public Health and the Environment (RIVM) to estimate chemical emissions from wastewater treatment plants (WWTPs) and exposure in surface water to support risk assessment of chemicals within the framework of environmental protection, has been a part of the European legislation for chemicals REACH (Registration, Evaluation and Authorization of Chemicals) since 2007 and is regarded to be an important tool applied in regulatory contexts and policy scenarios related to wastewater treatment (Struijs, 2015).

SimpleTreat enables the calculation of the fate of organic chemicals in a biological wastewater treatment plant with activated sludge. The model considers essential processes such as phase partitioning, degradation, and volatilization. The following physicalchemical properties need to be available for each compound: type of compound (neutral, base or acid), molecular weight, Know (or Dow and pKa for ionizable compounds), vapour pressure, water solubility, Henry's coefficient, Koc, partition coefficient in raw sludge (Kp_s), partition coefficient in activated sludge (Kp_{as}) and biodegradability. Experimentally determined data will significantly improve the robustness of the predictions. Suggested methodologies for determing these properties are available in the ECHA document ECHA-24-G-01-EN, Guidance on the Application of the CLP Criteria - Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures. It estimates concentrations of contaminants in effluents and sludge, as well as corresponding discharges through air, solid, and water from the WWTP (Struijs, 2014). It is possible to distinguish between WWTPs that have nitrification and those that don't by modifying the sludge age. The latest version is SimpleTreat 4.1 (November 2023) and is free to download for non-commercial use from the RIVM website. There is also an Excel version of the model (SimpleBoxTreat vs 4PAT) with the apparent latest update from 11.4.2023 and can be obtained by contacting the Association of Retired Environmental Scientists - ARES at the Radboud University Nijmegen (dvdm@retired-environmental-scientists.nl).

The SimpleTreat model is, as its name suggests, a very crude simple static model (assuming steady state and complete mixing of contaminants in nine WWTP "compartments") that provides a rough estimate of the fate of organic compounds during wastewater treatment. It is not possible to do a detailed tailoring of the variability of treatment trains found in different WWTPs but is possible to manipulate the most important factors influencing the partitioning and biodegradation during primary treatment and biological treatment. However, it does not include any chemical treatment step, which is very common in Norway, and it does not include any sludge treatment process. The latest versions have been adopted to

also manage polar and ionizable compounds, but there is still a limited validity for such compounds. The main challenge for many compounds is, however, to get hold of biodegradation data that sufficiently describes their fate in WWTPs.

4.1.6 Fate and behaviour in air

The data requirements set out for approval of PPPs (Regulation (EU) No 284/2013) define that this assessment depends on whether the trigger for volatilisation, Vp = 10^{-5} Pa (for volatilisation from plant) or 10^{-4} Pa (for volatilisation from soil) at a temperature of 20 °C is exceeded and (drift) mitigation measures are required to reduce exposure to non-target organisms. Model calculations of off-site deposition (PEC) originating from volatilisation is to be provided and the volatilisation term (PEC) shall be added into the relevant risk assessment procedures for PEC S and PEC SW.

Suitable estimations (calculations) of predicted environmental concentration, of active substance and metabolites, breakdown and reaction products is to be provided when relevant, and may include deposition of dust containing plant protection products by drift during sowing, indirect exposure of surface water via a sewage treatment plant (STP) after application of a plant protection product in storage rooms, and amenity use.

A 'worst case' PEC estimation is to be provided, relating to the maximum number and highest rates of application, at the shortest interval, for which authorisation is sought.

Under this section also belongs the potential for long-distance transport to be considered separately. Criteria that establish the potential for long-range environmental transport of an active substance safener or synergist include measurements and monitoring data establishing the occurrence of the substance at distant locations to its use (Kubiak et al., 2008). For a substance that migrates significantly through the air, its DT50 in air is to be greater than 2 days (Regulation 1107/2009).

Considerations for pesticide exposure in air has been developed by FOCUS (Kubiak et al., 2008) including both short range and long-range transport potential.

4.1.7 Norwegian/cold climate conditions

In VKM's assessments, there is a particular focus on possible increased persistence under Norwegian conditions (low temperatures). That is, low temperatures can cause a lesser degree of degradation. If it is not probable that the substance is completely degraded during one growing season, the substance is somewhat persistent and associated with a risk of accumulation in the soil after repeated use over several years. Current cut-off values include:

- A pesticide cannot be allowed to be used if the active substance (or metabolites) is present in the field more than one year; DT_{90} > 1 year and DT_{50} > 3 months, or
- If in the laboratory non-extractable residues constituting more than 70% of the original dose after 100 days concomitantly with a mineralisation < 5% in 100 days.

As mentioned above, field data (studying disappearance/dissipation) can be used, but these must be relevant to Norwegian conditions.

In principle, there are two different ways of conducting field experiments. The first is degradation studies and is used to calculate DegT50 from field studies. Decomposition in the top 30 cm is often referred to as $DegT50_{matrix}$. This study is designed to exclude as much as possible disruptive processes, so that one can get an expression of microbial degradation in soil. Processes that one wants to avoid include the effect of plants, photochemical decomposition, evaporation, and leaching. A group in EFSA has therefore proposed that the pesticide be incorporated into the top 10 cm. Others have suggested that sampling does not start until there is a certain amount of precipitation (50 mm). In this type of studies, a sampling is limited to the topsoil layers (50cm) making it unsuitable for mobile pesticides.

The second type of field studies is terrestrial field studies (TFD) and includes evaporation, effect of plant cover, evaporation, surface runoff and leaching to drainage water and groundwater. Values from TFD studies will therefore be difficult to use for modelling (see chapter 2.8 PEC in groundwater), but they nevertheless provide a measure of exposure. Field Dissipation may therefore result in shorter half-lives than laboratory degradation studies. In Canada, the USA and Mexico, TFD studies are required, while in the EU degradation studies are preferred, although TFD studies are most often delivered by manufacturers. However, attempts are being made to harmonize these methods to increase the transfer value for studies done in the EU and North America.

There must be a case-by-case assessment of how relevant the field data are for Norwegian conditions, based on parameters such as soil, precipitation, and temperature.

Important reference publications about Norwegian conditions to assess when performing an exposure and/or risk assessment of pesticides in the Norwegian environment, include but are not limited to the following:

- Degradation and mobility of pesticides in Norwegian soils. Opinion of the Panel on (or the Scientific Committee) of the Norwegian Scientific Committee for Food Safety (VKM, 2015).
- Establishing the representativeness of available surface water scenarios for plant protection products in environmental risk assessment in Norway. Opinion of the

Panel on Plant protection Products of the Norwegian Scientific Committee for Food and Environment (VKM et al., 2021).

- Norwegian Agricultural Environmental Monitoring Program (JOVA) annual and summary monitoring reports for pesticides in agricultural streams, available from www.nibio.no/jova. Reports from groundwater monitoring in Norwegian agricultural areas available at nibio.no/publikasjoner.

Further, joint procedures and guidelines for the approval process within the Northern Zone is outlined in the guidance document on work-sharing in the northern zone in the authorisation of plant protection products (Northern Zone, 2023) which is regularly updated. Section 20 Environmental fate and behaviour set out the core assessment requirements, guidelines and relevant cut-off values, and Appendix IV outline specific national requirements.

As mentioned in 4.1.4.2, from November 2023 the Norwegian Food Safety Authority have reduced the data requirements from 9 to 6 modelling scenarios for surface runoff. These changes will be implemented in the Northern Zone work-sharing-document in 2024. No national scenarios are included in the new requirements. The EU risk assessment for pesticides rely on standardized scenarios for transport modelling. These scenarios do not specifically represent Norwegian conditions and could in certain cases not provide sufficient protection for the Norwegian environment. A recent overall assessment pointed at temperature being the main deviating factor (VKM et al., 2021) when considering all available FOCUS modelling scenarios. The VKM PPP panel risk assessments should include a review of current methods available to improve the site-specificity of the assessment, as considering the major Norwegian agricultural soil types and the impact of soil texture and other soil characteristics on pesticide transport (Bolli et al., 2023; Holten et al., 2023; McGinley et al., 2022).

4.1.8 Biocides

Emission scenario documents (ESDs) are used to estimate the initial release of substances from biocidal products (or treated materials) to the environment. ESDs for several product types were developed in the EUBEES I and II projects. In addition, ESDs for some product types were developed by the OECD. All finalised ESDs for biocides are available at https://echa.europa.eu/guidance-documents/guidance-on-biocides-legislation/emission-scenario-documents, where the ESDs are presented per product type with relevant additional guidance and information.

Annex XIII to the REACH Regulation sets criteria for substances that are persistent, bioaccumulative and toxic (PBT) or very persistent and very bioaccumulative (vPvB). Under REACH, a PBT/vPvB assessment is required for all substances for which a chemical safety

assessment is carried out. A chemical safety assessment is required for substances manufactured or imported in amounts of 10 tonnes or more per year, unless exemptions apply. All biocidal active substances have to undergo a formal PBT assessment.

When assessing the persistence of substances, higher tier biodegradation tests in soil, sediment and/or surface water systems are required using standard OECD 307, 308 and 309 Test Guidelines (TGs), respectively.

A repository of detailed Technical Agreements for Biocides from the Environment Working group meetings is held at S-CIRCABC: https://webgate.ec.europa.eu/s-circabc/faces/jsp/extension/wai/navigation/container.jsp?FormPrincipal:_idcl=FormPrincipal:_id1&FormPrincipal_SUBMIT=1&id=20a938d6-b2c6-4876-840f-be4878ce8869&javax.faces.ViewState=9QYbDvk%2FHrLyWtQwMl4noxu0BEWEZsggJ6IJRQ2oqH%2Bkmb1TQS416MgaEuuz%2ByEeNtPnrzyUbstS7YYXP0M6%2BWrC%2Bdc9JV3PA6d%2B%2FYQzBtjaF%2F8yuBESCY4f6aW1EFPfrkMHf8%2FJa9vIqEdOOGRwxZ1gErQ%3D , and include guides on, among other:

- Cut-off criteria for GW assessment
- Lab leaching tests
- Semi field scale leaching test
- PEC sw and PEC sed
- Metabolites terrestrial compartment

Recent overviews for persistence/environmental fate studies further include:

- Critical literature review of **analytical methods** applicable to environmental studies (2021) (https://echa.europa.eu/documents/10162/17228/pfab_750_06_wp4_echa_final_report_en.pdf/b3a7e562-bf9c-ef02-948f-eaf1b8f89e3f?t=1616414618970)
- **Sterile controls** in biodegradation studies – current status in regulatory testing in persistence assessment under REACH (ECHA Note 2022) (https://echa.europa.eu/documents/10162/17228/note_sterile_controls_en.pdf/c5196c02-cdb6-e972-df94-5bc2c0b6d681?t=1669388792937)
- Options to assess persistence of **volatile substances** in regulatory PBT assessment (ECHA Note 2022) (https://echa.europa.eu/documents/10162/17228/note_volatiles_in_simulation_tests_en.pdf/d218ddcb-e5da-7c0a-e5d0-3eae3e1c26dc?t=1669388686441)
- Options to address **non-extractable residues** in regulatory persistence assessment (2019) (https://echa.europa.eu/documents/10162/17224/bg_note_addressing_non-

extractable_residues.pdf/e88d4fc6-a125-efb4-8278-d58b31a5d342?t=1565267847255)

The Biocidal Products Regulation has specific provisions for nanomaterials. The provisions apply to products and substances that meet the criteria defined in the Biocidal Products Regulation. These definitions are based on the Commission's recommendation on the definition of nanomaterials.

4.2 Ecotoxicology

If there is a possibility of exposure of birds and other terrestrial vertebrates, aquatic organisms, honeybees and other beneficial arthropods, earthworms and other non-target soil macroorganisms, or soil microbes to the plant protection product under the proposed conditions of use, the extent of acute and chronic risk for these organisms shall be evaluated. This includes an assessment of the risk posed by bioaccumulation (log Pow > 3) and endocrine disrupting properties. It may be necessary to conduct separate studies for metabolites, breakdown or reaction products derived from the active substance. Also, other authorised uses of plant protection products in the area of envisaged use containing the same active substance or which give rise to the same residues shall be taken into consideration. The potential impact of the active substance on biodiversity and the ecosystem, including potential indirect effects via alteration of the food web, shall be considered. Where appropriate and necessary, higher tier studies shall be supported by chemical analysis to verify exposure has occurred at an appropriate level.

In general, a risk quotient (RQ) is calculated. RQ can be expressed in several ways, for example as a toxicity:exposure ratio (TER) or as a hazard quotient (HQ). It may be associated to an SPG. Calculation method depends on the type of organism to be assessed. The EU has defined threshold values for the RQ in a three tiered acute and chronic risk assessment approach. If the threshold values are exceeded, approval shall not be granted unless it can be documented that these effects do not occur in a field situation in Norway.

The risk assessment procedure aims at protecting populations and may not protect e.g. individuals of rare species of birds and mammals.

The Northern Zone Guidance document describes the agreed procedure for assessing applications in the Northern Zone and covers guidance and amendments for national requirements, including ecotoxicology.

4.2.1 Birds and other terrestrial vertebrates

The EFSA guidance document for risk assessment for birds and mammals was published in 2009 (EFSA, 2009), and updated in 2010, containing screening and first-tier assessment procedures for a large range of scenarios, as well as general guidance for higher-tier assessments and on how to form an overall judgement on the level of risk. Furthermore, special care and considerations are to be taken when assessing (guidance document chapter 5): granular formulations, treated seeds, substances with ED properties, metabolites, exposure through drinking water, bioaccumulation & biomagnification.

Studies for risk assessment are not required if there is no risk of birds, mammals or other terrestrial vertebrates experiencing neither direct or secondary exposure to the active substance or plant protection product. Determination of acute oral toxicity of PPPs is required only if toxicity cannot be predicted on the basis of the data for the active substance, or where results from mammalian testing give evidence of higher toxicity of the plant protection product compared to the active substance. Indirect effects and over spraying of eggs of ground nesting birds are not covered by the guidance document risk assessment scheme.

An updated guidance document in 2023 outlines a tiered risk assessment scheme covering dietary exposure, exposure via secondary poisoning and exposure via intake of contaminated water (EFSA, Aagaard, et al., 2023). EFSA has also developed an online calculator which will implement the risk assessment methodology for all tiers of the risk assessment. It is not known when the 2023 updated guidance document will be implemented.

For higher tier risk assessments, the Northern Zone guidance document for higher tier risk assessment for birds and mammals and the associated spreadsheet/calculator tool must be used. In cases where PPPs contain more than one active substance, the Northern Zone mixtox calculator for birds and mammals must be used to address combined risk. All documents and tools can be found on the NFSA and/or the Danish EPA Northern Zone cooperation websites.

Birds

In addition to an initial acute and reproductive toxicity assessment with a quail species (use of mallard duck is no longer recommended), the risk assessment approach involves three tiers: screening with an indicator species, first-tier assessment with realistic exposure estimates and a generic focal species, and, if needed, a refined assessment with increased realism and a focal species approach.

As there are no defined SPGs for birds, the guidance first-tier assessment is designed to make mortality or reproductive effects unlikely. At higher tiers, a strict surrogate or actual protection goal (no mortality or effects on abundance/diversity) may be used, but this must be evaluated case by case. The EFSA guidance document provides detailed steps.

In the screening and first tier assessment, a calculated toxicity-exposure ratio (TER) is compared to a threshold value to evaluate risk and the need to assess the next tier. The aim of the screening is to highlight low risk substances and identify false negatives. The indicator species exposure estimate in this step therefore represents worst-case exposure assumptions. The first-tier risk assessment uses more realistic exposure estimates and is further refined by a generic focal species approach. A generic focal species is not a real species; however, it is considered to be representative of all those species potentially at risk.

The higher tier risk assessment involves a greater degree of realism and uses more realistic exposure estimates as well as a focal species approach: a real species that actually occurs in the crop when the pesticide is being used (there may be more than one focal species per crop). There are several refinement options for higher tier assessments, which may vary between member states.

Data describing the feeding habits and other ecological needs of indicator and general focal species, have been compiled in the EFSA guidance document, to be used directly in the exposure calculations. However, not all generic focal species (or focal species for higher tier assessments) are relevant for Northern Zone conditions. Therefore, the Northern Zone guidance document for pesticide risk assessment for birds and mammals must be consulted. This guidance document contains Northern Zone focal species relevant to different scenarios, crop types and its growth stages.

Mammals and other terrestrial vertebrates (reptiles and amphibians)

Information on terrestrial vertebrates other than birds shall be derived from the mammalian toxicological assessment, and acute oral toxicity determined. Reproductive toxicity to mammals shall be investigated, and the most sensitive endpoint reported (NOAEL) together with the EC10 and EC20. In the case of reptiles and amphibians, type and conditions of studies shall be discussed with the national competent authorities.

4.2.2 Aquatic organisms

4.2.2.1 Aquatic risks due to toxicity

Introduction

The "Guidance on tiered risk assessment for plant protection products for aquatic organisms in edge-of-field surface waters" was published in 2013 (EFSA PPR Panel (EFSA Panel on Plant Protection Products and their Residues), 2013) and endorsed as a guideline in 2015. A corrigendum was published in 2016 (EFSA PPR Panel (EFSA Panel on Plant Protection Products and their Residues), 2016).

In the Northern Zone, for the core assessment, a first-tier risk assessment in accordance with the EFSA Guidance document should be presented. The Northern Zone Guidance document further amends and refines the EFSA Guidance document on the higher tier risk assessment. In cases where PPPs contain more than one active substance, the Northern Zone aquatic mixtox tool must be used to address combined risk. Also, a live FAQ document related to mixtox calculations can be found on the Danish EPA Northern Zone cooperation website.

Specific protection goals (SPGs)

The overall level of protection of aquatic organisms is determined by the combination of the specific protection goals (SPGs) for the organisms and the exposure assessment goals. The overall aim of these SPGs is to protect aquatic plants and animals at the population level in surface water. However, the SPG selected for aquatic vertebrates aims at protection at the individual level, so that mortality and suffering due to acute toxicity is avoided.

Tiered approach

To protect populations of aquatic organisms, effect assessment schemes are developed that allow the derivation of Regulatory Acceptable Concentrations (RACs) on the basis of two effect assessment schemes, acute and chronic, aiming to protect aquatic populations, with options for negligible effects (ETO) or allowing recovery (ERO). Key steps include comparing adverse effects with maximum predicted concentrations and, for chronic effects, also considering time-weighted average concentrations. All tiers are able to address the ETO, while the model ecosystem approach (tier 3), under certain conditions (e.g. possibility to extrapolate observed responses to potential vulnerable species), is able to also address the ERO. Experimental approaches are prioritized over modeling, with future plans to address modeling in aquatic risk assessments (EFSA PPR Panel (EFSA Panel on Plant Protection Products and their Residues), 2013).

4.2.2.2 Tier 1 RAC_{sw} derivation on the basis of standard test species

Essential toxicity tests mandated for pesticides are detailed in the guidance document tables 1 to 3. Notably, tests involving algae and macrophytes are categorized under chronic Risk Assessment (RA) due to their comprehensive life cycle coverage, even though the selected toxicity endpoint is EC_{50}. A more comprehensive overview of tier 1 data requirements is provided in Chapter 7.

4.2.2.3 Tier 2 RAC_{sw} derivation on the basis of additional laboratory toxicity tests

Tier 2 RACsw derivation involves additional laboratory toxicity tests beyond basic data requirements. Three approaches are outlined in the guidance document (GD):

Tier 2A: **Geomean-AF approach** calculates Geomean $L(E)C_{50}$ or Geomean $NOEC/EC_{10}$ values for species within the same taxonomic group, applying an assessment factor (AF) from tier 1. However, if the most sensitive species deviates significantly from the geometric mean, a weight of evidence approach or further toxicity data generation is recommended.

Tier 2B: **Species Sensitivity Distribution (SSD)** approach derives median HC_5 and lower limit HC_5 values from SSD curves constructed with representative toxicity data for non-vertebrate or vertebrate species. For $RAC_{sw;ac}$ derivation, acute toxicity data of relevant taxonomic groups are utilized, while chronic toxicity data are used for $RAC_{sw;ch}$ derivation. The size of the AF is determined based on various factors including data quality, HC_5 values, and tier 1 and tier 3 RACs.

Tier 2C: **Refined Exposure Laboratory Test-AF** approach explores higher tier RAC derivation based on refined exposure laboratory tests if predicted exposure profiles significantly differ from standard toxicity studies. These tests should realistically simulate worst-case field exposure conditions and express RACs in terms of peak exposure concentration, compared with the maximum predicted environmental concentration ($PEC_{sw;max}$).

Tables 4, 5, 6, and 7 in the guidance document provide summaries and recommendations for each tier 2 approach, aiding in the derivation and use of RAC_{sw} in risk assessments for edge-of-field surface waters.

4.2.2.4 Tier 3 RAC_{sw} derivation on the basis of micro-/mesocosm tests

The process of deriving Tier 3 Risk Assessment Concentration for Surface Water (RAC_{sw}) from micro-/mesocosm tests involves evaluating the test system, experimental setup, exposure regime, endpoints, and statistical/ecological relevance. Decision Scheme C outlines effect classes for endpoint evaluation. The EFSA's PPR Panel provides procedures for deriving ETO-RAC_{sw} and ERO-RAC_{sw}, ideally from the same study. Assessment Factors (AF) size determination is crucial, and guidance is provided in the guidance document.

4.2.2.5 Bioconcentration and secondary poisoning

To assess the risk of secondary poisoning for birds and mammals consuming fish from water contaminated with a potentially problematic compound, regulatory acceptable concentrations (RAC_{sp}) are determined. These RAC_{sp} values are compared with the 21-day time-weighted average predicted environmental concentrations in surface water (TWA PEC_{sw}) to evaluate potential risks.

4.2.2.6 Metabolites and degradation products

The PPR Panel's assessment scheme for metabolites involves determining the presence of toxophores and conducting testing accordingly. Metabolites with toxophores require testing, focusing on sensitive taxa. If toxophores are absent, toxicity is compared to the parent compound, with further testing if necessary. Endocrine disruption and bioaccumulation potential are also evaluated. Overall, the scheme ensures comprehensive risk assessment tailored to metabolite characteristics.

4.2.3 Bees and non-target arthropods

Bees (Honeybees, bumblebees and solitary bees)

The Commission guidance from 2002 (Commission guidance, 2022) remains the basis for conducting the risk assessment for pesticides to bees, and with this, also EPPO's "Environmental risk assessment scheme for Plant Protection Products —chapter 10: honeybees" (EPPO / OEPP et al., 2010) revised in September 2010 with ICPBR5 recommendations. The modified EPPO procedure should be applied for chronic risk assessment for adult honeybees from spray applications (ECPA, 2017). EFSA published a specific bee guidance document in 2013 (EFSA, 2013). Since 2013, a majority of Member States have consistently objected to an endorsement. In particular to the parts related to chronic toxicity for honeybees, bumblebees and solitary bees. On 11 May 2023, EFSA published its latest revised guidance document (EFSA, Adriaanse, et al., 2023), covering honeybees, bumblebees, and solitary bees. Also, supplementary information (EFSA, C., et al., 2023)to the revised guidance was published on the same date.

The endorsing procedure of the revised guideline was started in May 2023. This includes updating EU 546/2011 (which still lists HQ (exposure/toxicity) values for honeybees of 50), and possibly also EU 283/2013 and EU 284/2013. Only when this is finished, the guidance document can be endorsed. Regulation updates may finish at the earliest spring 2024. The date of endorsement of the guidance document will then be discussed among the member states. Work is also ongoing on additional test guidelines for pollinators.

See the EC web page (European Commission, 2024b) for latest developments of the bee guidance document.

Endorsed guideline: Guidance Document on Terrestrial Ecotoxicology, 2002

There are no specific protection goals (SPGs) in the 2002 guidance document.

Honeybees (Commission guidance 2002 & EPPO 2010)

If honeybees are likely to be exposed to the active substance (including residues and/or metabolites in nectar, pollen and water) both acute (oral and contact) and chronic toxicity tests must be conducted. However, where there is only one relevant route of exposure, testing can be restricted to this exposure route. If sub-lethal effects on growth or development cannot be excluded, a bee brood study shall also be carried out. Tests for sub-lethal effects (such as behavioral and reproductive effects) on colonies may be required.

Bumblebees and solitary bees (guideline not endorsed)

In cases of potential exposure of bees for the representative use, field studies on bumblebees and solitary bees would always be needed, unless:

- the lower tier risk assessments for honeybees and non-target arthropods other than bees show no effects for the active substance, or
- semi-field (cage or tunnel studies) with bumblebees and solitary bees show absence of effects.

Furthermore, semi-field or field testing with bumblebees would also not be needed if laboratory studies according to OECD test methods No 246 and 247, show an LD50 > 100 µg active substance/bumblebee.

Tiered approach

For risk assessment of effects on bees, a risk assessment form has been developed by EPPO (EPPO / OEPP et al., 2010) where a step-by-step procedure is proposed.

First tier assessment

Requirements are the same for assessments of PPPs and active substances.

According to the guideline (2002) and EU 284/2013, acute toxicity tests should be conducted according to EPPO 170, or OECD 213 and OECD 214 guidelines, providing LD_{50} and NOEC oral and contact values. Hazard quotients for spray oral (HQo) and contact exposure (HQc) are calculated as the maximum applied dose (g a.s./ha) divided by oral or contact LD_{50}, respectively. For solid formulations, a TER for oral exposure is calculated. If HQo or HQc >50 (spray), or TER < 10 (soil or seed treatment), higher tier testing is required.

A bee brood study shall provide the EC_{10}, EC_{20}, EC_{50} and NOEC for honeybee larvae, and adult bees, where possible. The test method of Oomen et al. (1992) is recommended as a worst-case screening test. In the case of effects, further cage/tent/tunnel or field studies are necessary to evaluate the risk under more realistic conditions. The bee brood study is not necessary if toxicity to broods can be predicted already from the compound MOA.

Chronic oral toxicity shall be provided for active substance and PPP as EC_{10}, EC_{20}, EC_{50} and NOEC. All results shall be given as µg a.s./bee.

Second tier assessment

The second-tier assessments include refinements of the first-tier tests, including the bee brood study for larvae and adult bees, as well as supplementary tests and data. Also, residue tests should be included: A toxicity test in which worker honeybees are fed treated sucrose for 10 days to calculate a 10-day NOEL (mg a.s. per bee perday) should be provided. The TER should be calculated with the NOEL from the 10-day chronic toxicity test in bees and/or the measured level of residues in the relevant material for honeybees (mean residue data).

Higher tier assessment

Higher tier studies may be conducted as semi-field (cage, tent, tunnel) or field studies. According to the guideline (2002), the recommendations of EPPO guideline 170 (EPPO, 2024) should be taken into account. Semi-field trials or tunnel tests are experiments in which bees are introduced into a culture covered with a tent.

Field trial requirements with associated expert assessment are triggered to assess whether there are indications of effects such as reduced activity or modified behavior in bees. There are no clearly defined endpoints for higher tier. The parameters considered should be relevant to the compound under consideration.

Revised guideline (draft 2023)

Specific Protection Goals

There is a challenge defining Specific Protection Goals (SPGs) for the generic protection goal of "unacceptable effects" in Regulation (EC) No 1107/2009. EFSA proposed a methodology based on ecosystem services and biodiversity, and the SPGs for honeybees are based on EFSA technical reports on background variability of honeybee colony sizes. Through consultations and dialogue, risk managers agreed on a 10% maximum permitted colony size reduction for honeybees (*A. mellifera*) after pesticide exposure. This value is very ambitious compared to what is acceptable under the 2002 Guidance (HQ<50). However, an evidence-

based threshold for bumble bees and solitary bees couldn't be established due to data limitations, resulting in an "undefined threshold." EFSA therefore continues to update the bee guidance document. The finalized SPGs are outlined in Table 4.2.3.

Table 4.2.3. **Overview of the agreed SPGs for honeybees, bumble bees and solitary bees**

Dimensions	Honeybees	Bumble bees	Solitary bees
Ecological Entities	Colony	Colony	Population
Attribute	Colony strength**	Colony strength**	Population abundance
Magnitude*	≤ 10%	Undefined	Undefined
Temporal scale	Any time	Any time	Any time
Spatial scale	Edge of field	Edge of field	Edge of field

*: This was the only dimension reviewed and agreed by risk managers. The definition of the other dimensions was retained as in (EFSA, 2013). For bumble bees and solitary bees, a defined threshold will be decided by risk managers when more data becomes available.

**: Operationalized as colony size reduction

This means in practice that field studies on wild bees (bumblebees, solitary bees) will be required unless lower tier risk assessments for honeybees and non-target arthropods other than bees show no effects, or semi-field (cage or tunnel) with wild bees show absence of effects. Furthermore, semi-field or field tests with bumblebees is not needed if laboratory studies (OECD No 246 & 247) shown an LD50>100 ug active substance/bumblebee.

Risk assessments

The revised guidance document brings several novelties to the risk assessment process:

- Refined exposure scenarios (chapter 4; e.g. no-water scenarios, amendments to off-field scenarios, weed abundance considerations, triggering the succeeding crop scenario).
- Full dose-response hazard characterization (chapter 6), no point estimates (LD50, NOEC, etc.). Also, methodologies for deriving a surrogate dose-response (i.e. limit tests or where maximum observed effect is below 10%), taking time-course effects into account, and extrapolating from honeybees to other bee groups are available.
- Two general unified threshold models of survival (GUTS) are applied to account for time-reinforced toxicity (chapter 8 on TRT; accumulative toxicity in EFSA 2013).
- Regarding sublethal effects (chapter 9), there is only focus on effects on foraging behavior and in honeybees only. The HPG assessment (hypopharyngeal glands development) is not included anymore. There was no documented link between effects on HPG and colony strength (SPG), and no internationally agreed guidelines

for testing. Field studies are still based on existing guidance (EPPO 170), but with new statistical requirements and SPG linked to colony strength to be studied as a main endpoint in a field realistic setup. Also, SPG for bumblebees and solitary bees are suggested with proposed assessment methods.
- A new scheme for technical mixtures and metabolites.
- A calculator web tool is under development, to be available for the implementation of the revised guideline.

Other non-target arthropods

Effects on non-target terrestrial arthropods shall be investigated for all PPPs except in situations where non-target arthropods are not exposed. Testing is nevertheless required if the PPP contains more than one active substance, and/or the toxicity of a PPP cannot be reliably predicted to be either the same or lower than the active substance tested.

Data on two sensitive standard species as well as data on two crop relevant species are required. If effects are observed with species relevant to the proposed use, then further testing may be required. The assessment of risk for arthropods living in- and off-field is conducted separately and should be adequately addressed. Where significant effects have been observed, the toxicity of the product to two additional species must be investigated.

In 2000, a guidance document for assessing the risk to non-target arthropods, was produced from a workshop attended by all EU Member States as well as representatives from industry and academia (Candolfi et al., 2001; ESCORT 2, 2000).

For the first tier, data from glass-plate tests on two standard sensitive species is required: the cereal aphid parasitoid *Aphidius rhopalosiphi*, and the predatory mite *Typhlodromus pyri*. A rate-response study (LR50; lethal rate) is usually required, which is compared to the predicted exposure both in-field and off-field. Also, NOEC should be reported.

This standard approach is not appropriate for substances with limited solubility or for plant protection products such as granules, seed treatments and pellets. In these cases, studies should be conducted with *Hypoaspis aculeifer* or *Folsomia candida*. If appropriate, studies with *Aleochara sp*. may be conducted, e.g. at tier 2. For substances suspected to have a special mode of action (IGRs, insect feeding inhibitors), tests should include sublethal endpoints, sensitive life stages, special routes of uptake or other appropriate modifications. Higher-tier tests (extended laboratory tests, aged-residue studies, semi-field tests, field tests) are required when a risk is indicated in lower assessment tiers.

Generally, exposure for non-target arthropods is expressed in terms of application rate (g/ha or ml/ha) multiplied by a multiple application factor (MAF), drift factor and/or vegetation distribution factor.

If the resulting 'hazard quotient' (HQ) based on the standard tests is greater than or equal to 2, then further data (higher tier) and/or risk management measures are required.

- In-field HQ = in-field exposure / LR50
- Off-field HQ = (off-field exposure / LR50) * correction factor (usually 10)

Risk mitigation options within the cropped area are application frequency and intervals, timing of application and unsprayed headlands. In off-field areas, buffer zones, wind breaks and drift-reducing application techniques may be modified.

Arthropods may also be exposed to metabolites in/on plants and to soil metabolites. Standard lab tests are then normally not required, except in cases where for example the metabolite is the pesticidal active molecule. Soil metabolites are assessed with regards to soil organisms, so that tests with soilsurface arthropods are not needed.

For further details on methods, exposure, and risk assessment, see the ESCORT 2 document.

4.2.4 Earthworms, and other soil non-target organisms (macro and micro)

The currently endorsed guideline is the "Guidance document on terrestrial ecotoxicology under Council Directive 91/414/EEC" from 2002, as refined by the Northern Zone guidance document.

The guideline outlines a systematic approach to assess the impact of active substances on soil macro-organisms, focusing on those involved in organic matter breakdown. It suggests tiered testing based on substance persistence, with methods such as the Collembola reproduction test and litter bag test. Risk assessment for earthworms and soil micro-organisms is a tiered approach based on toxicity exposure ratios and their thresholds.

Acute effects on earthworm

Tests for acute effects are not required for active substances nor PPPs. In the guidance document (2002) and previous directive 91/414/EEC, tests for acute effects (OECD 207; ISO 11268-1: 1993) was always required where contamination of the soil was possible, and sublethal tests were required if the assessment of the acute risk gave a TER of less than 10.

Chronic / Sublethal effects on earthworms
For active substances, a test, providing information on the sublethal effects on growth, reproduction, and behavior of the earthworm (dose-response, EC10, EC20, NOEC), is always required where contamination of the soil is possible (OECD 222; ISO 11268-2: 1998). The test must be performed under controlled conditions to predicted environmental concentrations in soil (PECsoil). Organic carbon content of the medium and the lipophilic properties of the test substance must be considered. In the guidance document (2002) and previous directive 91/414/EEC, certain triggers (exposure pattern, degradation time) were put forward for when sublethal tests were required. This practice was however repealed by 1107/2009.

If the toxicity of a PPP cannot be predicted based on data for the active substance, and exposure of earthworms to the PPP cannot be excluded, a two-tiered risk assessment is required. For the first tier, a test, providing information on the effects on growth and reproduction of the earthworm (dose-response, EC10, EC20, NOEC) is required.

Earthworm field studies
Field studies may not be required for active substances.

If laboratory sublethal tests indicates a chronic risk of a PPP, field studies must be performed to assess potential effects under more realistic conditions (use, environmental conditions, species; ISO 11268-3:1999). Soil analysis should confirm the exposure relevancy.

Effects on non-target soil meso- and macrofauna (other than earthworms)
Effects on soil organisms, other than earthworms, shall be investigated for all test substances, except in situations where soil organisms are not exposed.

For foliar spray applications, data on *Folsomia candida* and *Hypoaspis aculeifer* may be required by national authorities. Direct soil treatments (spray or solid formulation) should be tested on both *F. candida* (OECD 232; ISO 11267) and *H. aculeifer* (OECD 226) establishing dose-response, EC10, EC20, and NOEC, also considering exposure, organic carbon content (f_{oc}), and lipophilic properties of the test substance (K_{ow}).

For PPPs, realistic higher tier tests (community/population/field) are required where significant effects are seen following species level testing.

4.2.5 Soil nitrogen transformation and terrestrial non-target higher plants

Tests for impact on soil nitrogen transformation (OECD 216) are required when active substances or plant protection products containing the substance are applied to soil or could contaminate it, and the toxicity of the plant protection product cannot be predicted on the basis of data for the active substance. Carbon transformation tests are no longer necessary. For soil sterilization products, studies must focus on recovery rates after treatment. Test conditions mandate the use of fresh agricultural soils untreated with substances altering microbial populations in the past two years, except transiently.

Risk assessment of non-target plants follows a three-tiered approach: initial decision based on screening data, quantitative assessment using the TER approach, and higher-tier assessment based on field studies. Acceptable risk thresholds are determined based on deterministic or probabilistic methods. Risk mitigation options include buffer zones and drift-reducing application techniques.

Sufficient screening data for evaluating effects on six species and families of non-target plants, particularly herbicidal or growth regulatory activity, must be provided. Non-target plants are defined as those outside the treatment area. Test conditions should mimic field use or consider residue accumulation. Tests are mandated if screening studies lack necessary coverage, providing ER50 values, especially for substances with herbicidal or growth regulatory activity. Tests for vegetative vigor and seedling emergence on at least six species are necessary, representing diverse taxonomic groups. However, data are exempt for substances with minimal exposure, like those used in controlled environments or specific applications.

Reporting of effects of PPPs on non-target plants is required if toxicity cannot be predicted from the active substance data. Extended laboratory studies may be required if a high risk is identified, providing information on potential effects following more realistic exposure. Semi-field and field tests can be submitted for a refined risk assessment, addressing effects on plant abundance and biomass production at varying distances from the crop.

4.2.6 Other non-target organisms (flora and fauna)

Any available data on the effects of the active substance or plant protection product on other terrestrial organisms shall be submitted.

4.2.7 Bacterial activity in wastewater treatment plants

There are no guidance documents from EFSA or ECHA related to the assessment of potential inhibition of the biological treatment step at wastewater treatment plants from pesticides or their transformation products. Any compound in the wastewater entering a WWTP with a biological treatment step may influence the overall bacterial activity, whether it is biodegraded or not. A toxic compound not meant to be in the wastewater may inhibit the activity of one or more bacterial enzymes if the concentration is high enough and/or the exposure time is long enough. The inhibition can be competitive (binds to the enzyme in the same place as the substrate), non-competitive (binds somewhere else on the enzyme preventing the product from being formed) and un-competitive (binds to the active complex formed from the substrate blocking the product from forming). Which type of inhibition that is effective in each case can be determined from Lineweaver-Burk plots (1/r_s vs 1/S), Hanes plots (S/r vs S) or Eadie-Hofstee plots (r_s/S vs r_s) (Orozco 2008). Recognized protocols for carrying out inhibition tests are the NS-EN ISO 8192:2007 Test for inhibition of oxygen consumption by activated sludge for carbonaceous and ammonium oxidation and the OECD Test No. 209 Activated Sludge, Respiration Inhibition Test (Carbon and Ammonium Oxidation), the latter being based on the former and the Ecological and Toxicological Association of the Dyestuffs Manufacturing industry (ETAD) test (Brown et al., 1981). These are both short term exposure tests (30-180 min) measuring the effect on the bacterial respiration (oxygen uptake rate). If the WWTP is applying biological nitrogen removal, the potential inhibition of the nitrifying bacteria should be assessed using NS-EN ISO 9509:2006 Toxicity test for assessing the inhibition of nitrification of activated sludge microorganisms. The exposure times are usually somewhat longer (3-24 hours).

The methods describe a synthetic wastewater medium to be used (based on peptone and meat or comparable vegetable extract) in combination with fresh activated sludge from "a well-operated wastewater treatment plant receiving predominantly domestic sewage". As pointed out by (Henze et al., 2002), complex formation, chemical precipitation and biodegradation make it difficult to evaluate the toxic effects, and these depend to a large degree on the type of wastewater and inoculum being used in the test. Moreover, if the WWTP has been exposed to this chemical for å prolonged period, the activated sludge may have been substantially adapted to its presence and may significantly impact the observed inhibition. Hence, results obtained with a standard medium and a "typical" inoculum will not necessarily be able to predict the actual inhibition risk posing an actual WWTP. However, for a general assessment, the standard medium and a non-adapted inoculum should be used in tests.

There are no guidelines or standard methods for assessing inhibition of anaerobic processes at WWTPs, neither the very common mesophilic anaerobic digestion nor anaerobic wastewater treatment.

5 Novel Pesticides

5.1 Low-Risk pesticides (incl. Microbials, botanicals and basic substances)

An active substance can be approved as a low-risk substance if it meets the regular approval criteria and in addition meets the low-risk criteria as specified in Annex II, point 5 of Regulation (EC) 1107/2009 (Commission Regulation (EC) No 1107/2009, 2009). Most of the low-risk criteria are linked to toxicity and bioaccumulation, but a substance shall also not be considered as of low risk if persistent with a half-life in soil is more than 60 days. There are specific criteria for chemical substances and for micro-organisms.

The initial definition of low-risk pesticides set out in Regulation (EC) 1107/2009 was amended in Regulation (EU) 2017/1432 to '*reflect the current state of scientific and technical knowledge'.* This being specified as (a.o.):

- *The criteria pertaining to persistence and bioconcentration, in light of current scientific and technical knowledge, could prevent approval as low-risk substances, of certain naturally occurring substances presenting considerably less of a risk than other active substances, such as certain botanicals or minerals. It is therefore appropriate to allow for the approval of such substances as being of low-risk, in cases where they comply with Article 22 of Regulation (EC) No 1107/2009*.
- *Semio-chemicals, which are substances emitted by plants, animals and other organisms which are used for intra- and inter-species communication, have a target-specific and non-toxic mode of action and are naturally occurring. They are generally effective at very low rates, often comparable to levels that occur naturally. In light of current scientific and technical knowledge it is also appropriate to provide that semio-chemicals should be considered as low-risk substances*.
- *Active substances in the meaning of Article 2 of Regulation (EC) No 1107/2009 include micro-organisms whose properties differ from those of chemical substances. It is appropriate that the low-risk criteria applicable to micro-organisms are provided for based on the current scientific and technical knowledge.*

The development and placing on the market of low-risk substances and products is encouraged by several regulatory incentives. Low-risk substances are approved for 15 years

instead of 10 years and data protection on the studies submitted for the approval and subsequent authorisation is prolonged from 10 to 13 years. Moreover, a fast-track authorisation procedure with reduced timelines (120 days instead of one year) ensures that low-risk products can be placed on the market quickly.

For more information on the substances approved as low-risk substances, see the EU Pesticides Database (https://food.ec.europa.eu/plants/pesticides/eu-pesticides-database_en).

The current risk assessment procedures are not optimal for low risk pesticides, and the recently (2022) initiated EU project RATION (https://www.ration-lrp.eu/) aims to develop a novel, concrete and research-based risk assessment scheme, supported by the necessary guidance on methods and tools, tailored to the specific characteristics of established and emerging LRP solutions (i.e. currently available LRPs (microbials, plant extracts, pheromones, semiochemicals) and emerging LRPs (e.g., RNA interference (RNAi) based pesticides, microbiome solutions)). However, no Nordic zone countries are participants in this work.

5.1.1 Microbials

From 21 November 2022 new requirements for approval of micro-organisms and plant protection products ("PPPs") containing micro-organism apply through the four EU implementing Regulations amending the existing legal framework applicable to PPPs:

- Regulation (EU) 2022/1438, which amends Regulation (EC) No 1107/2009 concerning the placing of plant protection products on the market ("PPPR") and, in particular, its Annex II which lies down the procedure and criteria for the approval of active substances.
- Regulation (EU) 2022/1439, which amends Regulation (EU) No 283/2013 setting out the data requirements for active substances.
- Regulation (EU) 2022/1440, which amends Regulation (EU) No 284/2013 setting out the data requirements for plant protection products.
- Regulation (EU) 2022/1441, which amends Regulation (EU) No 546/2011 setting out the uniform principles for evaluation and authorisation of PPPs.

5.1.2 Basic substances

Basic substances are substances that are not predominantly used for plant protection purposes but may be useful in plant protection. They are substances of no concern and can be approved for plant protection use as far as their risks are acceptable. Some of these

substances have been traditionally used by farmers and may include foodstuffs. Examples are vinegar, sucrose or calcium hydroxide. Their approval by the Commission allows the use for purposes of plant protection, but they cannot be sold specifically as a plant protection product. Approval criteria for basic substances are given in Regulation 1107/2009 Article 23.

The rules governing the procedure of approval apply as set out in the following document: Working document on the procedure for application of basic substances to be approved in compliance with Article 23 of Regulation (EC) No 1107/2009; SANCO/10363/2012 rev.11. Based on the description of the intended uses, the potential consequences of increased exposure with respect to natural exposure levels of water, soil or air or to exposure due to other uses should be considered. An estimation of the predicted environmental concentrations in soil, water (both surface and groundwater) and air resulting from the intended uses should be given. For naturally occurring substances, the predicted environmental concentrations should be compared to the natural background concentrations. It should be demonstrated that the substance will not have "an unacceptable effect on the environment". Data requirements are as set out in Regulations (EU) 283/2013 (active substances) and 284/2013 (PPPs) regarding the calculation of predicted environmental concentrations.

The legal frameworks under which substances are regulated in accordance with other Union legislation provide for specific approval criteria and may differ in the level of protection of human or animal health and the environment. In the assessment of basic substances for use as PPPs, the level of protection of human and animal health and the environment as ensured by the PPP Regulation will be taken as a reference. More information on the approval of basic substances; https://food.ec.europa.eu/plants/pesticides/approval-active-substances_en.

5.2 Nano-pesticides

Nano-pesticides is a rapidly developing tool which is anticipated to become available also in Norwegian agriculture with the goals and needs to reduce the use of chemical pesticides. The current regulatory framework is not sufficiently adapted/developed to assess the environmental exposure (and effects) of nano-pesticides. Currently available guidance documents and scientific reviews include:

- **Guidance** on risk assessment of nanomaterials to be applied in the food and feed chain: human and animal health (2021) (https://www.efsa.europa.eu/en/efsajournal/pub/6768)

- Comprehensive **framework** for human health risk assessment of nanopesticides (2021)
  (Kah et al 2021; https://www.nature.com/articles/s41565-021-00964-7)
- A critical **evaluation** of nanopesticides and nanofertilizers against their conventional analogues (2018)
  (Kah et al 2018; https://www.nature.com/articles/s41565-018-0131-1)
- Nanopesticides: **State** of Knowledge, Environmental Fate, and Exposure Modeling (Kah et al. 2013;
  (https://www.tandfonline.com/doi/full/10.1080/10643389.2012.671750)
- Analysing the fate of nanopesticides **in soil** and the applicability of regulatory protocols using a polymer-based nanoformulation of atrazine
  (Kah et a. 2014; https://link.springer.com/article/10.1007/s11356-014-2523-6)
- **An overview** of nanopesticides in the framework of European legislation (2017)
  (Villaverde et al. 2017;
  https://www.sciencedirect.com/science/article/abs/pii/B9780128042991000072?via%3Dihub)

The above mentioned EFSA guidance on risk assessment of nanomaterials to be applied in the food and feed chain: human and animal health (EFSA 2021) elaborates on physico-chemical characterization, methods and techniques that can be used for characterization of nanomaterials and their determination in complex matrices and additionally provides details on hazard identification and characterization as well as exposure assessment.

Testing shall be performed according to the methods described in regulation 440/2008 for REACH, but when test methods are applied to nanomaterial, an explanation shall be provided of their scientific appropriateness for nanomaterial, and where applicable, of the technical adaptations/adjustments that have been made in order to respond to the specific characteristics of these materials (828/2012, Annex II).

5.3 Safeners, synergists, co-formulants

Requirements for the approval of Safeners, synergists and co-formulants are included in the current regulations for active substances and PPPs. Further details on data requirements and identification criteria include the following:

- A draft regulation for data requirements for safeners and synergists is currently under public (Draft regulation – Ares (2023)7954663). Commission adoption is planned for first quarter 2024.
- Plant protection products (PPP) are mixtures composed of one or more active substance(s) and co-formulants that facilitate handling/application, even distribution

on the plants and/or improve storage and product/user safety (such as solvents, carriers, wetting agents, dyes, etc.). Co-formulants that cannot be used in plant protection products because of the harmful effects of their use and/or residues on human health or the environment are listed in Annex III to Regulation (EC) No 1107/2009. Rules and criteria for the identification of other unacceptable co-formulants are available in Commission Implementing Regulation (EU) 2023/574 (European Commission, 2024a).

- "3.6.2. An active substance, safener or synergist shall only be approved if, on the basis of assessment of higher tier genotoxicity testing carried out in accordance with the data requirements for the active substances, safeners or synergists and other available data and information, including a review of the scientific literature, reviewed by the Authority, it is not or has not to be classified, in accordance with the provisions of Regulation (EC) No 1272/2008, as mutagen category 1A or 1B."

Uncertainties

The process of identifying limitations in scientific knowledge and evaluating their implications for scientific conclusions is vital in all risk assessments, thus EFSA published a guidance document on uncertainty analysis in 2018 (EFSA Scientific Committee et al., 2018). Additionally, VKM routinely discovers and summarises knowledge and data gaps in our risk assessment processes as these relate to uncertainties in our conclusions (VKM 2022).

The current document is to serve as a reference document for the risk assessment work of the VKM PPP panel. The accuracy of the document depends on continuous/regular update to reflect changes in the regulatory framework and the available scientific evidence or relevance for the risk assessment of active substances and PPPs. At present its content reflects the regulatory framework in sufficient accuracy and detail, while we see that the search for relevant scientific literature performed when preparing the document was somewhat hampered by the selection of search phrases and search engines. Obvious lacks in the material of scientific reviews retrieved have been remedied by ad-hoc searches, but this work was not sufficient (or aimed) to complete the picture. When performing risk assessments, the available scientific literature will be reviewed for the topic in question and, hence, any lacks in this methods document will not impact the quality of any future risk assessments performed. Systematic review is a core methodology in the current approach of risk assessments performed by VKM. The PPP panel should further strive to include relevant methods for assessing risk of bias in available scientific publications when performing risk assessments.

Conclusions (with answers to the terms of reference)

The current document is to serve as a reference document for the risk assessment work of the VKM PPP panel, and at present its content reflects the regulatory framework in sufficient accuracy and detail. When performing risk assessments, the available scientific literature will be reviewed for the topic in question and, hence, any lacks in this methods document will not impact the quality of any future risk assessments performed.

The major changes and novel aspects in this methodology document as compared with the 2012 version include:

General:

- The document refers to the current version (last updated September 2023) of the Guidance document on work-sharing in the northern zone in the authorization of plant protection products, for a detailed overview of the specific requirements set out for Norway or jointly for the Northern zone countries. Norway joined this collaboration as a full partner upon the adoption of the EU PPP regulations in 2015.
- More detailed information about the data requirements and methods for risk assessment of novel types of pesticides, like low-risk pesticides and nano-pesticides, have been added to the document. Possible data gaps and needs for revised risk assessment methodologies are commented where relevant.
- A simplified approval process and risk assessment procedure for microbials was adopted in 2022 through Regulations (EU) 2022/1438, 1439, 1440, and 1441.
- Proposed (revised) data requirements for safeners and synergists have been added (Draft regulation – Ares (2023) 7954663).
- Data requirements and methods for the risk assessment of biocides have been added to the document.

Human toxicology:

- European Chemical Agency (ECHA) and European Food Safety Authority (EFSA) with the technical support of the Joint Research Centre (JRC), published a guidance document in 2018 on how to identify substances with endocrine disrupting properties in pesticides and biocides. This guidance document outlines the scientific criteria for hazard identification, which are based on Commission Delegated Regulation (EU)

2017/2100 for biocidal products and Commission Regulation (EU) 2018/605 for plant protection products.
- Opening for use of alternative methods to decrease toxicological testing in animals.
- For non-dietary exposure, EFSA issued a guidance on the assessment of exposure of operators, workers, residents, and bystanders to harmonize the methodology and datasets used in this area of risk assessment of PPPs in 2014. Prior to this, the member states employed varying datasets and models.

Environmental fate:

- Aged sorption is described in more detail and refers to the current guideline (SANTE/12586/2020 – REV 0 (26 January 2021)) for handling this as part of the core assessment in the Northern Zone (Northern Zone, 2023).
- Recent additions to the knowledge about environmental fate of pesticides under Norwegian conditions have been included, with 'Degradation and mobility of pesticides in Norwegian soils' (VKM, 2015) and 'Establishing the representativeness of available surface water scenarios for plant protection products in environmental risk assessment in Norway' (VKM et al., 2021) as key reference publications.
- The Norwegian Food Safety Authority have recently (November 2023) reduced the modelling scenarios required for approval in Norway reduced from 9 to 6 FOCUS scenarios for surface runoff.
- Relevant aspects pertaining to drinking water treatment and wastewater treatment plants have been added to the document.

Ecotoxicology:

- Regarding aquatic risks due to toxicity, EFSA published a guidance in 2013 and introduced the implementation of specific protection goals (SPGs) aimed to protect both individual aquatic vertebrates from acute toxicity and populations of aquatic plants and animals in surface water in 2015. The tiered approach for effect assessment schemes allows for the derivation of Regulatory Acceptable Concentrations (RACs) based on acute and chronic effects.
- In 2023, EFSA published a revised guidance document covering honeybees, bumblebees, and solitary bees. The endorsement procedure of the revised guideline is in progress. Regulation updates is expected to be completed at the earliest spring 2024.
- The guidance document on risk assessment for birds and mammals from 2009, was updated in 2023. However, the updated guidance is not yet implemented. The new guidance document outlines a tiered risk assessment scheme covering dietary

exposure, exposure via secondary poisoning and exposure via intake of contaminated water. EFSA has also developed an online calculator.

- Bacterial activity in wastewater treatment plants.

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Appendix I

Working document

Document

Appendix II

Scientific literature search strategy

Document