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Understanding of 'negligible exposure' in international science, policy and law, and qualification of the term in relation to the exposure of endocrine substances to the environment

To support the interpretation of 3.8.2 of Annex II of Regulation (EC) No 1107/2009

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Abstract: Understanding of 'negligible exposure' in international science, policy and law, and qualification of the term in relation to the exposure of endocrine substances to the environment

This report aims to clarify the term "negligible exposure" to endocrine disruptors in context of European plant protection product regulations. A thorough research of scientific, policy and legal literature was performed. It yielded 3,087 publications released between 2010 and 2023, 204 of which predominantly focused on the use and understanding of the term in environmental and human health. Definitions of "negligible exposure" were extracted from a sub-group of 49 publications related to (chemical) substances in the environment.

Findings were grouped into narrative, qualitative, and quantitative definitions of the term. Narrative definitions paraphrased "negligible" as insignificant, meaningless, of no importance or not worth considering. Qualitative and quantitative definitions were more intricate and context-dependent and defined negligible concentrations/exposures/effects using low values, values below the limit of detection, and comparators as a control, a benchmark, or a legal threshold.

From these findings, a definition of "negligible exposure of endocrine disruptors to the environment" was derived, which depends on the results of the identification and environmental risk assessment of endocrine active substances and their uncertainties. A quantitative definition can be applied to exposures of endocrine active substances to species, where modes of action are known and test methods are available, allowing for an acceptable level of uncertainty (risk-based approach). For increased uncertainty, a definition tending to prevent endocrine active substances from entering the environment by restricting their uses to closed systems (hazard-based approach) would be more appropriate.

Kurzbeschreibung: Verständnis des Begriffs "vernachlässigbare Exposition" in der internationalen Wissenschaft, Politik und Gesetzgebung sowie Definition des Begriffs in Bezug auf die Exposition von endokrinen Substanzen in der Umwelt

Dieses Gutachten zielt darauf ab, den Begriff „vernachlässigbare Exposition" gegenüber endokrinen Disruptoren im Zusammenhang mit den europäischen Pflanzenschutzmittelverordnungen zu klären. Es wurde eine gründliche Recherche der wissenschaftlichen, politischen und rechtlichen Literatur durchgeführt. Sie resultierte in 3.087 zwischen 2010 und 2023 veröffentlichten Publikationen, von denen sich 204 überwiegend auf die Verwendung und das Verständnis des Begriffs in den Bereichen Umwelt und menschliche Gesundheit konzentrierten. Definitionen des Begriffs „vernachlässigbare Exposition" wurden aus einer Untergruppe von 49 Veröffentlichungen zu (chemischen) Stoffen in der Umwelt extrahiert.

Die Ergebnisse wurden nach narrativen, qualitativen und quantitativen Definitionen des Begriffs gruppiert. Narrative Definitionen umschrieben „vernachlässigbar" als nicht signifikant, unwichtig, ohne Bedeutung oder nicht bedenkenswert. Qualitative und quantitative Definitionen waren komplizierter und kontextabhängig und definierten vernachlässigbare Konzentrationen/Expositionen/Auswirkungen anhand von niedrigen Werten, Werten unterhalb der Nachweisgrenze und Vergleichswerten wie einer Kontrolle, einem Benchmark oder einem gesetzlichen Schwellenwert.

Aus diesen Erkenntnissen wurde eine Definition der „vernachlässigbaren Exposition von endokrin aktiven Substanzen" abgeleitet, die von den Ergebnissen der Identifizierung und Umweltrisikobewertung dieser Stoffe und deren Unsicherheiten abhängt. Eine quantitative Definition kann auf die Exposition endokrin aktiver Stoffe gegenüber Arten angewandt werden, bei denen die Wirkungsweise bekannt ist und Testmethoden zur Verfügung stehen, die ein akzeptables Maß an Unsicherheit zulassen (risikobasierter Ansatz). Bei größerer Ungewissheit ist eine

Definition angemessener, die darauf abzielt zu verhindern, dass endokrin wirksame Stoffe in die Umwelt gelangen, indem ihre Verwendung auf geschlossene Systeme beschränkt wird (gefahrenbasierter Ansatz).

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List of abbreviations

ADME	absorption, distribution, metabolism, and excretion
BMD	benchmark dose
BMR	benchmark risk
CAB	Centre for Agriculture and Bioscience
EC	European Commission
EC_{50}	median effect concentration
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
ECHA	European Chemicals Agency
ED	endocrine disruptor
EFSA	European Food Safety Authority
EPA	Environmental Protection Agency
EQS	Environmental Quality Standards
ETR	exposure toxicity ratio
EU	European Union
FT	full text
LC_{50}	median lethal dose
LOAEL	lowest observed adverse effect level
LOD	limit of detection
LOEC	lowest observed effect concentration
LOQ	limit of quantification
MoA	mode of action
MPCs	maximum permissible concentrations
MRL	maximum residue limit
NCs	negligible concentrations
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NTOs	non-target organisms
PEC	predicted environmental concentration
PICO	population, intervention, control, outcome
PNEC	predicted no-effect concentration
PPP	plant protection products
PRISMA	preferred reporting items for systematic reviews and meta-analyses
QSARs	quantitative structure-activity relationship models
RAC	regulatory acceptable concentrations
RQ_{NCs}	risk quotient of negligible concentrations
T/A	title/abstract
UBA	German Environment Agency (Umweltbundesamt)

WHO	World Health Organization
WoS	Web of Science
WTO	World Trade Organization

Summary

Background

Regulation (EC) No. 1107/2009 mandates that any active substance, safener, or synergist must be approved only if tests, in line with Community or internationally accepted guidelines, confirm that it does not harbour any adverse endocrine-disrupting properties that may harm non-target organisms (NTOs). The European Union (EU) has established scientific criteria to determine endocrine-disrupting properties via Regulation (EC) 2018/605 and Implementing Regulation (EC) 2018/1659 (EC, 2018a, 2018b). These guidelines are employed in the evaluation of plant protection products (PPP).

However, Regulation (EC) No. 1107/2009 allows for two exceptions: one, when the active substance is needed to combat a serious risk to plant health, and two, when the exposure of NTOs to the active substance in a PPP, under proposed realistic conditions of use, is "negligible". For human health, the Regulation defines "negligible exposure" as the use of the product in closed systems or other conditions that prevent human contact and ensure residues of the substance in food and feed don't exceed the default value set by Article 18(1)(b) of Regulation (EC) No. 396/2005. However, terms like "negligible," "closed system", or "contact with humans" lack clear definitions, especially concerning the environment.

The European Commission (EC), DG SANTE, the Directorate-General for Health and Food Safety, drafted a Technical Guidance Document (EC, 2015) to aid interpretation of these terms. The document suggests assessing human exposure using identified Maximum Residue Levels (MRLs) and non-dietary exposure through risk mitigation measures, natural background levels, or safety margins. However, the document doesn't offer a starting point for environmental exposure assessment.

Aim of the report

The aim of the report is to describe the use and definition of the terms "negligible", "no exposure", "negligible exposure", and "negligible concentration" in scientific literature, policy and law. Based on this, manageable criteria and feasible measures are to be worked out to define "negligible exposure of non-target organisms to active substances/ endocrine disruptors".

Methodology

A systematic literature search was conducted to identify national and international literature (including primary studies, reviews, and grey literature) that explore the concepts of "negligible", "no exposure", "negligible exposure", and "negligible concentration". This search was based on the principles of a scoping review, which is an exploratory research method aimed at mapping key concepts, types of evidence, and identifying research gaps in a defined field. The methodology of scoping reviews is not as rigorously outlined as systematic reviews, but some methodological publications have set a standard.

The research strategy was initially defined in a study protocol. The key points defined were: key criteria such as Population, Intervention, Control, Outcome (PICO); search areas (including databases and Google); search terms and strings; inclusion and exclusion criteria (time, country, and language of publication, type of publication, and access); protocol for documentation, tables, and data extraction; review team, time and work plan, tools.

Four searches were executed, considering synonyms for searches 3 and 4. Searches 1 and 2 sought to analyse the broader usage of "negligible" and "no exposure" and were therefore performed in multidisciplinary database Scopus, Google, and legal databases. Due to their inability to process comprehensive search strings, Google and LawInsider were not used for searches 3

and 4. Three additional search runs were performed using an advanced Google search to find definitions for the term "closed system".

The search was limited to life science subject areas, English-language publications from 2010 onwards, and where full texts were available. Included were primary, secondary, and grey literature. The criteria for inclusion and exclusion were set, specifying the subject areas, year of publication, language, country of publication, type of publication, and accessibility of full text.

The literature search was conducted extensively in English in electronic databases with a scientific or legal focus, including PubMed, Scopus, Web of Science (WoS), CAB Direct (CAB), LIVIVO, LawInsider, and EUR-Lex. For grey literature, an advanced Google search was performed according to BioMath standard operating procedure. A backward reference search was also conducted with key publications post literature database and grey literature searches.

Search results were collected and categorized using reference management software, Citavi 6. Information such as the source, type of publication, online address, and bibliographic information was included. The search results from different databases were combined and duplicates removed.

The study selection was a two-step process: firstly, title and abstract screening was performed against the inclusion criteria, and then the full texts of the manuscripts were examined. The selection was primarily based on defined key criteria and the suitability of the studies, particularly the presentation and clarity of the term "negligible". This process is represented in a flow chart following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) protocol.

Data extraction involved collecting various elements from the selected publications, such as condition, context, method, subject area, and type of definition. This allowed for a systematic approach to definitions and interpretations of the terms "negligible", "no exposure", "negligible exposure", and "negligible concentration".

The extracted data were synthesized into a structured summary based on the definitions and interpretations of the terms. Certain publications of unique significance were identified as key publications. The extraction process highlighted the methods used to define negligibility and, where applicable, compiled corresponding values or additional information related to these methods.

The final step discussed the transferability of the definitions to environmental negligible exposure of endocrine disruptors.

Results

The literature review, conducted from April 3rd to 6th, 2023, identified 3,087 publications across diverse databases and search methods. After eliminating 895 duplicates and applying pre-defined protocol criteria, a pool of 2,192 publications was screened, focusing on aspects such as publication type, year, language, and relevance. The majority, 1,419 publications, were disregarded due to non-alignment with set criteria. The resulting literature was assigned to one of 21 subject areas, with only publications from life sciences or those providing dictionary definitions considered pertinent and retained. Subsequent full-text screening led to the exclusion of additional 569 publications, culminating in a selection of 204 life science-oriented publications for inclusion in the study.

Out of the 3,087 identified publications, the single search term "negligible" in search 1 yielded the most findings (1,282). Yet, it should be noted that duplicates found across the four sequential searches were generally attributed to the later search, resulting in a possibly inflated success

rate for search 1. The 204 selected life science publications were predominantly assigned to environment (64) and human health (57) subject areas. Consistent with the exclusion criteria, all included publications were released between 2010 and 2023. Nevertheless, four pre-2010 publications that were identified in the additional manual search were incorporated due to their high relevance. Most of the selected publications date back to 2020 and 2021, with dictionaries representing exceptions when the year of publication was not available. Additional categorization of these 204 publications was undertaken, examining aspects such as type, concept, and relevance to "negligible" in relation to a substance. A sub-group of 49 publications, relating to (chemical) substances in the environmental subject area, was further singled out for comprehensive examination in subsequent sections. All 204 publications, along with their categories and brief descriptions, are catalogued in the appendix.

The uses and understandings of "negligible", "no exposure", "negligible exposure", and "negligible concentration" were exhaustively examined, primarily through their specific applications across various fields. These were organized into three types: narrative, qualitative, and quantitative definitions. Narrative definitions, primarily sourced from dictionaries, paraphrase the meaning of a term. Qualitative definitions present specific criteria or qualitative descriptors like "no", "very low", or "not observed". Quantitative definitions provide a numerical value or a range. In both regulatory and scientific realms, the ranking of these definitions generally follows: narrative < qualitative < quantitative. Most of the 204 selected publications adhere to quantitative definitions.

A review of 23 dictionary entries demonstrated that the term "negligible" typically refers to something so minute, unimportant, or insignificant that it is inconsequential and can be disregarded. The identified definitions fell into two principal categories: Lack of Worth or Insignificance, which centres around something being so trivial or unimportant that it can be safely ignored, and Quantitative Minutia, highlighting the term's use in quantifying the minimal extent or probability of something. Therefore, "negligible" is consistently interpreted to signify something of such small significance or unimportance that it lacks worth and can be overlooked, applicable across various contexts.

In the process of exploring definitions for "negligible exposure", it becomes clear that the concept of "exposure" is closely related to the "concentration" of a substance and its potential "effects". In this context, "concentration" signifies the quantity of a substance in a specific environmental medium, while "exposure" refers to the level of a substance encountered by an organism, factoring in frequency, duration, and route of exposure. The "effect", in turn, refers to the biological changes resulting from exposure. Various related terms are also mentioned, each intertwining with the core concepts of concentration, exposure, and effect. These definitions form the basis for subsequent examination of the findings from the 49 reviewed publications.

Transferability of results

Quantitative definition of negligible exposure corresponds to a risk-based approach which places emphasis on assessing and managing the risks of the chemical in use and keeping possible exposure below thresholds (for instance through exposure mitigation). Nevertheless, such a definition is implementable only for endocrine active substances and species where hazard, exposure as well as Modes of Action (MoA) are known, and validated test methods are available. Also, negligible exposure can only be defined quantitatively for chemicals where there is agreement on a toxicological threshold for endocrine-mediated adverse effects.

If hazard, exposure or MoA are not known or test methods are not available it is not possible to agree on toxicological thresholds for endocrine-mediated adverse effects. Negligible exposure then only can be described narratively - as to being nearly zero exposure – and ensured only by

excluding or minimising contact. Corresponding to a hazard-based approach emphasis is placed on limiting the exposure by using active substances in closed or by targeted systems.

A claim of negligible exposure exemption typically follows the identification of an endocrine disruptor. Consequently, the results of endocrine activity and effect from this identification serve as the foundation for an exposure assessment, and the adequacy of existing data determines the applicability of quantitative threshold definitions.

Conclusions and recommendations

Both quantitative and qualitative definitions presuppose the impracticality of zero tolerance and the availability of knowledge on a substance's hazard and exposure. Nevertheless, both narrative and qualitative definitions should be avoided because these terms can be considered vague and not resilient.

Based on the findings of the review, definitions of "negligible exposure of non-target organisms to active substances/ endocrine disruptors" in the frame of Regulation (EC) No 1107/2009 were worked out, based on the comprehensive environmental risk assessment of substances to identify endocrine disruptive substance properties.

- Exposure is understood to be negligible if demonstrated to be below toxicologically relevant thresholds for the representative uses. This approach requires comprehensive knowledge on a substance's hazard and exposure. For endocrine active substances this can only be demonstrated to non-target organisms, where MoAs are known, test systems and Regulatory Acceptable Concentrations (RAC) are available, and low-dose effects with non-monotonic dose-response relationships are excluded.
- Exposure is understood to be negligible if uses are restricted to closed systems. This approach requires knowledge on the equipment and isolation potential of such systems. Gradually more or less closed systems have different isolation potential, only stationary, floored structures (greenhouses, closed buildings) have the safest isolation properties. This approach is even applicable, if negligible exposure cannot be demonstrated quantitatively to be below toxicologically relevant thresholds for the representative uses.

Zusammenfassung

Hintergrund

Die Verordnung (EG) Nr. 1107/2009 schreibt vor, dass ein Wirkstoff, Safener oder Synergist nur dann zugelassen werden darf, wenn Tests im Einklang mit gemeinschaftlichen oder international anerkannten Leitlinien bestätigen, dass er keine schädlichen endokrinen Eigenschaften aufweist, die Nichtzielorganismen (NTO) schaden könnten. Die Europäische Union (EU) hat mit der Verordnung (EG) 2018/605 und der Durchführungsverordnung (EG) 2018/1659 wissenschaftliche Kriterien zur Bestimmung der endokrin schädlichen Eigenschaften festgelegt. Diese Leitlinien werden bei der Bewertung von Pflanzenschutzmitteln angewendet (EC, 2018a, 2018b).

Die Verordnung (EG) Nr. 1107/2009 lässt jedoch zwei Ausnahmen zu: erstens, wenn der Wirkstoff zur Bekämpfung eines ernsten Risikos für die Pflanzengesundheit erforderlich ist, und zweitens, wenn die Exposition von NTOs gegenüber dem Wirkstoff in einem PSM unter den vorgeschlagenen realistischen Anwendungsbedingungen „vernachlässigbar" ist. Im Hinblick auf die menschliche Gesundheit definiert die Verordnung „vernachlässigbare Exposition" als die Verwendung des Produkts in geschlossenen Systemen oder unter anderen Bedingungen, die den Kontakt mit Menschen verhindern und sicherstellen, dass die Rückstände des Wirkstoffs in Lebens- und Futtermitteln den in Artikel 18 Absatz 1 Buchstabe b der Verordnung (EG) Nr. 396/2005 festgelegten Standardwert nicht überschreiten. Begriffe wie „vernachlässigbar", „geschlossenes System" oder „Kontakt mit dem Menschen" sind jedoch nicht klar definiert, insbesondere in Bezug auf die Umwelt.

Die Europäische Kommission, GD SANTE, die generaldirektion Gesundheit und Lebensmittelsicherheit, hat einen technischen Leitfaden (EC, 2015) verfasst, um die Auslegung dieser Begriffe zu erleichtern. Das Dokument schlägt vor, die Exposition des Menschen anhand von festgelegten Rückstandshöchstgehalten (MRL) und der Exposition außerhalb der Ernährung durch Risikominderungsmaßnahmen, natürliche Hintergrundwerte oder Sicherheitsmargen zu bewerten. Das Dokument bietet jedoch keinen Ansatzpunkt für die Bewertung der Umweltexposition.

Ziel des Gutachtens

Ziel des Gutachtens ist es, die Verwendung und Definition der Begriffe „vernachlässigbar", „keine Exposition", „vernachlässigbare Exposition" und „vernachlässigbare Konzentration" in der wissenschaftlichen Literatur, der Politik und dem Recht zu beschreiben. Darauf aufbauend sollen handhabbare Kriterien und praktikable Maßnahmen zur Definition der „vernachlässigbaren Exposition von Nicht-Zielorganismen gegenüber Wirkstoffen/endokrinen Disruptoren" erarbeitet werden.

Methodik

Es wurde eine systematische Literaturrecherche durchgeführt, um nationale und internationale Literatur (einschließlich Primärstudien, Übersichten und grauer Literatur) zu identifizieren, die die Konzepte „vernachlässigbar", „keine Exposition", „vernachlässigbare Exposition" und „vernachlässigbare Konzentration" untersucht. Diese Suche basierte auf den Prinzipien eines Scoping Reviews, einer explorativen Forschungsmethode, die darauf abzielt, Schlüsselkonzepte und Arten von Belegen zu erfassen und Forschungslücken in einem bestimmten Bereich zu identifizieren. Die Methodik von Scoping-Reviews ist nicht so streng umrissen wie bei systematischen Reviews, aber einige methodologische Veröffentlichungen haben einen Standard gesetzt.

Die Recherchestrategie wurde zunächst in einem Studienprotokoll festgelegt. Als Eckpunkte wurden festgelegt: Schlüsselkriterien wie Population, Intervention, Control, Outcome (PICO); Suchbereiche (u.a. Datenbanken und Google); Suchbegriffe und -strings; Ein- und

Ausschlusskriterien (Zeitpunkt, Land und Sprache der Veröffentlichung, Art der Veröffentlichung und Zugang); Protokoll für Dokumentation, Tabellen und Datenextraktion; Review-Team, Zeit- und Arbeitsplan, Tools.

Es wurden vier Recherchen durchgeführt, wobei für die Recherchen 3 und 4 auch Synonyme berücksichtigt wurden. Die Recherchen 1 und 2 zielten darauf ab, die breitere Verwendung von „vernachlässigbar" und „keine Exposition" zu analysieren, und wurden daher in den multidisziplinären Datenbanken Scopus, Google und juristischen Datenbanken durchgeführt. Da Google und LawInsider keine umfassenden Suchbegriffe verarbeiten können, wurden diese nicht für die Recherchen 3 und 4 verwendet. Drei weitere Suchläufe wurden mit einer erweiterten Google-Suche durchgeführt, um Definitionen für den Begriff „geschlossenes System" zu finden.

Die Suche beschränkte sich auf lebenswissenschaftliche Fachgebiete, englischsprachige Publikationen ab 2010, deren Volltexte verfügbar waren. Eingeschlossen wurden Primär-, Sekundär- und graue Literatur. Es wurden Ein- und Ausschlusskriterien festgelegt, die die Themenbereiche, das Erscheinungsjahr, die Sprache, das Land der Veröffentlichung, die Art der Veröffentlichung und die Zugänglichkeit des Volltextes spezifizierten.

Die Literaturrecherche erfolgte umfassend in englischer Sprache in elektronischen Datenbanken mit naturwissenschaftlichem oder juristischem Schwerpunkt, darunter PubMed, Scopus, Web of Science (WoS), CAB Direct (CAB), LIVIVO, LawInsider und EUR-Lex. Für graue Literatur wurde eine erweiterte Google-Suche gemäß dem Standardarbeitsverfahren von BioMath durchgeführt. Außerdem wurde eine Rückwärtssuche mit den wichtigsten Veröffentlichungen nach der Suche in der Literaturdatenbank und der grauen Literatur durchgeführt.

Die Suchergebnisse wurden mit der Literaturverwaltungssoftware Citavi 6 erfasst und kategorisiert. Informationen wie Quelle, Art der Publikation, Online-Adresse und bibliografische Angaben wurden aufgenommen. Die Suchergebnisse aus verschiedenen Datenbanken wurden kombiniert und Duplikate entfernt.

Die Studienauswahl erfolgte in zwei Schritten: Zunächst wurde ein Titel- und Abstract-Screening anhand der Einschlusskriterien durchgeführt, anschließend wurden die Volltexte der Manuskripte geprüft. Die Auswahl basierte in erster Linie auf definierten Schlüsselkriterien und der Eignung der Studien, insbesondere der Darstellung und Klarheit des Begriffs „vernachlässigbar". Dieser Prozess ist in einem Flussdiagramm nach dem PRISMA-Protokoll (Preferred Reporting Items for Systematic reviews and Meta-Analyses) dargestellt.

Bei der Datenextraktion wurden verschiedene Elemente aus den ausgewählten Veröffentlichungen gesammelt, wie z. B. Zustand, Kontext, Methode, Themenbereich und Art der Definition. Dies ermöglichte eine systematische Herangehensweise an Definitionen und Interpretationen der Begriffe „vernachlässigbar", „keine Exposition", „vernachlässigbare Exposition" und „vernachlässigbare Konzentration".

Die extrahierten Daten wurden auf der Grundlage der Definitionen und Interpretationen der Begriffe in einer strukturierten Zusammenfassung synopsiert. Bestimmte Publikationen von einzigartiger Bedeutung wurden als Schlüsselpublikationen identifiziert. Bei der Extraktion wurden die zur Definition der Vernachlässigbarkeit verwendeten Methoden hervorgehoben und gegebenenfalls entsprechende Werte oder zusätzliche Informationen zu diesen Methoden zusammengestellt.

Im letzten Schritt wurde die Übertragbarkeit der Definitionen auf die vernachlässigbare Umweltexposition gegenüber endokrinen Disruptoren erörtert.

Ergebnisse

Bei der Literaturrecherche, die vom 3. bis 6. April 2023 durchgeführt wurde, wurden 3.087 Veröffentlichungen in verschiedenen Datenbanken und Suchmethoden gefunden. Nach der Eliminierung von 895 Duplikaten und der Anwendung vordefinierter Protokollkriterien wurde ein Pool von 2.192 Publikationen gescreent, wobei der Schwerpunkt auf Aspekten wie Publikationstyp, Jahr, Sprache und Relevanz lag. Die meisten, nämlich 1.419 Publikationen, wurden aufgrund der Nichtübereinstimmung mit den festgelegten Kriterien nicht berücksichtigt. Die daraus resultierende Literatur wurde einem von 21 Themenbereichen zugeordnet, wobei nur Veröffentlichungen aus den Lebenswissenschaften oder solche, die Wörterbuchdefinitionen liefern, als relevant angesehen und beibehalten wurden. Ein anschließendes Volltextscreening führte zum Ausschluss von weiteren 569 Publikationen, so dass schließlich 204 lebenswissenschaftlich orientierte Publikationen in die Studie aufgenommen wurden.

Von den 3.087 identifizierten Veröffentlichungen lieferte der einzelne Suchbegriff „vernachlässigbar" in Suche 1 die meisten Ergebnisse (1.282). Es ist jedoch zu beachten, dass die in den vier aufeinanderfolgenden Suchen gefundenen Duplikate in der Regel der späteren Suche zugeordnet wurden, was zu einer möglicherweise überhöhten Erfolgsquote für Suche 1 führt. Die 204 ausgewählten biowissenschaftlichen Veröffentlichungen wurden überwiegend den Themenbereichen Umwelt (64) und menschliche Gesundheit (57) zugeordnet. In Übereinstimmung mit den Ausschlusskriterien wurden alle einbezogenen Publikationen zwischen 2010 und 2023 veröffentlicht. Dennoch wurden vier Publikationen aus der Zeit vor 2010, die bei der zusätzlichen manuellen Suche identifiziert wurden, aufgrund ihrer hohen Relevanz einbezogen. Die meisten der ausgewählten Publikationen stammen aus den Jahren 2020 und 2021, wobei Wörterbücher Ausnahmen darstellen, wenn das Jahr der Veröffentlichung nicht verfügbar war. Diese 204 Publikationen wurden zusätzlich kategorisiert, wobei Aspekte wie Art, Konzept und Relevanz für „vernachlässigbar" in Bezug auf einen Stoff untersucht wurden. Eine Untergruppe von 49 Veröffentlichungen, die sich auf (chemische) Stoffe im Umweltbereich beziehen, wurde für eine umfassende Untersuchung in den folgenden Abschnitten herausgefiltert. Alle 204 Publikationen sind mit ihren Kategorien und Kurzbeschreibungen im Anhang katalogisiert.

Die Verwendung und das Verständnis von „vernachlässigbar", „keine Exposition", „vernachlässigbare Exposition" und „vernachlässigbare Konzentration" wurden eingehend untersucht, vor allem anhand ihrer spezifischen Anwendungen in verschiedenen Bereichen. Es wurden drei Typen identifiziert: narrative, qualitative und quantitative Definitionen. Narrative Definitionen, die hauptsächlich aus Wörterbüchern stammen, umschreiben die Bedeutung eines Begriffs. Qualitative Definitionen enthalten spezifische Kriterien oder qualitative Deskriptoren wie „kein", „sehr gering" oder „nicht beobachtet". Quantitative Definitionen geben einen numerischen Wert oder einen Bereich an. Sowohl im regulatorischen als auch im wissenschaftlichen Bereich gilt für diese Definitionen im Allgemeinen folgende Rangfolge: narrativ < qualitativ < quantitativ. Die meisten der 204 ausgewählten Veröffentlichungen halten sich an quantitative Definitionen.

Eine Durchsicht von 23 Wörterbucheinträgen hat gezeigt, dass der Begriff „vernachlässigbar" sich in der Regel auf etwas bezieht, das so winzig, unwichtig oder unbedeutend ist, dass es belanglos ist und vernachlässigt werden kann. Die ermittelten Definitionen lassen sich in zwei Hauptkategorien einteilen: Geringfügigkeit oder Unbedeutendheit, wobei es darum geht, dass etwas so trivial oder unwichtig ist, dass man es getrost vernachlässigen kann, und Quantitative Minutia, wobei der Begriff zur Quantifizierung des minimalen Ausmaßes oder der minimalen Wahrscheinlichkeit einer Sache verwendet wird. Daher wird „vernachlässigbar" durchgängig so interpretiert, dass etwas von so geringer Bedeutung oder Unwichtigkeit ist, dass es keinen Wert hat und übersehen werden kann, was für verschiedene Kontexte gilt.

Bei der Untersuchung von Definitionen für „vernachlässigbare Exposition" wird deutlich, dass das Konzept der „Exposition" eng mit der „Konzentration" eines Stoffes und seinen potenziellen „Wirkungen" zusammenhängt. In diesem Zusammenhang bedeutet „Konzentration" die Menge eines Stoffes in einem bestimmten Umweltmedium, während sich „Exposition" auf die Menge eines Stoffes bezieht, mit der ein Organismus in Berührung kommt, wobei Häufigkeit, Dauer und Weg der Exposition berücksichtigt werden. Die „Wirkung" wiederum bezieht sich auf die biologischen Veränderungen, die sich aus der Exposition ergeben. Diese Definitionen bilden die Grundlage für die anschließende Untersuchung der Ergebnisse aus den 49 überprüften Veröffentlichungen.

Übertragbarkeit der Ergebnisse

Die quantitative Definition der vernachlässigbaren Exposition entspricht einem risikobasierten Ansatz, bei dem der Schwerpunkt auf der Bewertung und dem Management der Risiken der verwendeten Chemikalie liegt und die mögliche Exposition unter den Schwellenwerten gehalten wird (z. B. durch Expositionsminderung). Eine solche Definition ist jedoch nur für endokrin aktive Stoffe und Arten umsetzbar, bei denen die Gefahr, die Exposition und die Wirkungsweise bekannt sind und valide Testmethoden zur Verfügung stehen. Außerdem kann eine vernachlässigbare Exposition nur quantitativ für Chemikalien definiert werden, bei denen eine Einigung über einen toxikologischen Schwellenwert für endokrin vermittelte schädliche Wirkungen besteht.

Wenn Gefahr, Exposition oder MoA nicht bekannt sind oder keine Testmethoden zur Verfügung stehen, ist es nicht möglich, sich auf toxikologische Schwellenwerte für endokrin vermittelte schädliche Wirkungen zu einigen. Eine vernachlässigbare Exposition kann dann nur narrativ beschrieben werden - im Sinne von nahezu Null-Exposition - und nur durch Ausschluss oder Minimierung des Kontakts sichergestellt werden. Entsprechend einem gefahrenbasierten Ansatz wird der Schwerpunkt auf die Begrenzung der Exposition durch die Verwendung von Wirkstoffen in geschlossenen oder abgeschirmten Systemen gelegt.

Die Untersuchung, ob eine Exposition vernachlässigbar sei, folgt in der Regel auf die Identifizierung eines endokrinen Disruptors. Folglich dienen die Ergebnisse der endokrinen Aktivität und Wirkung aus dieser Identifizierung als Grundlage für eine Expositionsbewertung, und die Angemessenheit der vorhandenen Daten bestimmt die Anwendbarkeit von quantitativen Schwellenwertdefinitionen.

Schlussfolgerungen und Empfehlungen

Sowohl quantitative als auch qualitative Definitionen setzen voraus, dass eine Nulltoleranz nicht praktikabel ist und dass Kenntnisse über die Gefährlichkeit und die Exposition eines Stoffes vorhanden sind. Dennoch sollten sowohl narrative als auch qualitative Definitionen vermieden werden, da diese Begriffe als vage und nicht belastbar angesehen werden können.

Auf der Grundlage der Ergebnisse der Recherche wurden Definitionen für die „vernachlässigbare Exposition von Nichtzielorganismen gegenüber Wirkstoffen/endokrinen Disruptoren" im Rahmen der Verordnung (EG) Nr. 1107/2009 erarbeitet, die auf der umfassenden Umweltverträglichkeitsprüfung von Stoffen zur Identifizierung endokrin wirksamer Stoffeigenschaften basieren.

- Die Exposition wird als vernachlässigbar angesehen, wenn sie nachweislich unterhalb der toxikologisch relevanten Schwellenwerte für die repräsentativen Verwendungen liegt. Dieser Ansatz erfordert umfassende Kenntnisse über die Gefahr und die Exposition eines Stoffes. Bei endokrin wirksamen Stoffen kann dies nur an Nichtzielorganismen nachgewiesen werden, wenn die Grenzwerte bekannt sind, Prüfsysteme und behördlich anerkannte

Konzentrationshöchstgrenzen zur Verfügung stehen und Wirkungen bei niedrigen Dosen mit nicht monotonen Dosis-Wirkungs-Beziehungen ausgeschlossen sind.

- Die Exposition wird als vernachlässigbar angesehen, wenn die Verwendung auf geschlossene Systeme beschränkt ist. Dieser Ansatz erfordert Kenntnisse über die Ausrüstung und das Isolationspotenzial solcher Systeme. Mehr oder weniger geschlossene Systeme haben ein graduell unterschiedliches Isolationspotenzial, nur stationäre, bodengestützte Strukturen (Gewächshäuser, geschlossene Gebäude) haben die sichersten Isolationseigenschaften. Dieser Ansatz ist auch dann anwendbar, wenn nicht quantitativ nachgewiesen werden kann, dass die vernachlässigbare Exposition unter den toxikologisch relevanten Schwellenwerten für die repräsentativen Verwendungen liegt.

1 Introduction

1.1 Background

According to Regulation (EC) No. 1107/2009, Annex II, 3.8.2, "an active substance, safener or synergist ... is approved only if it is determined, on the basis of the evaluation of tests carried out in accordance with Community or internationally accepted test guidelines, that it does not possess any adverse endocrine disrupting properties that may cause adverse effects on non-target organisms". For determining endocrine disrupting (ED) properties, the European Union (EU) has established scientific criteria in Regulation (EC) 2018/605 and Implementing Regulation (EC) 2018/1659 (EC, 2018a, 2018b). These criteria are to be applied in the evaluation of plant protection products (PPP) as of November 10, 2018.

Nevertheless, Regulation (EC) No 1107/2009 provides two possibilities for derogation: when the active substance is to be used to control serious risk to plant health (Art. 4(7)) and when the exposure of non-target organisms (NTOs) to that active substance in a plant protection product, under realistic proposed conditions of use, is "negligible".

With respect to human health, the Regulation defines negligible exposure as "the product is used in closed systems or in other conditions excluding contact with humans and where residues of the active substance, safener or synergist concerned in food and feed do not exceed the default value established in accordance with Article 18(1)(b) of Regulation (EC) No 396/2005". Regarding the environment, the Regulation does not define the term, but allows for an authorisation if "the exposure of NTOs to that active substance in a plant protection product [...] is negligible under realistic proposed conditions of use". The term "negligible" itself is not defined, and neither are the terms "closed system" or "contact with humans".

To provide guidance regarding the interpretations of these wordings, the European Commission (EC), DG SANCTE, the Directorate-General for Health and Food Safety, has drafted a Technical Guidance Document (EC, 2015). In relation to the default values for the assessment of human exposure mentioned in the regulation, it is proposed to perform the assessment of dietary exposure using identified Maximum Residue Levels (MRLs) and the assessment of non-dietary exposure using risk mitigation measures, natural background levels, or safety margins. However, the guidance does not provide starting points for environmental exposure assessment.

1.2 Aim of this report

The aim of the report is to describe the use and definition of the terms "negligible", "no exposure", "negligible exposure", and "negligible concentration" in scientific literature, policy and law. Based on this, manageable criteria and feasible measures are to be worked out to define "negligible exposure of non-target organisms to active substances/ endocrine disruptors".

2 Methodology: Literature search

A search to identify national and international relevant literature (primary studies, reviews, grey literature, etc.) that address the concepts of "negligible", "no exposure", "negligible exposure", and "negligible concentration" was conducted according to the principles of a scoping review.

As a method of knowledge synthesis, scoping reviews have the potential to advance practice, policy, and research. A scoping review "addresses an exploratory research question aimed at mapping key concepts, types of evidence, and gaps in research related to a defined area or field by systematically searching, selecting, and synthesising existing knowledge" (Colquhoun et al., 2014). At a general level, scoping studies might "aim to map rapidly the key concepts underpinning a research area and the main sources and types of evidence available and can be undertaken as stand-alone projects in their own right, especially where an area is complex or has not been reviewed comprehensively before" (Arksey & O'Malley, 2005). Scoping reviews search and select the literature in the same systematic way as systematic reviews. The methodology of scoping reviews is not as strongly laid down in guidelines as is the case for systematic reviews. Nevertheless, some methodological publications have become standard (Arksey & O'Malley, 2005; Bragge et al., 2011; Daudt, van Mossel, & Scott, 2013; Hidalgo Landa et al., 2011; Levac, Colquhoun, & O'Brien, 2010; Miake-Lye, Hempel, Shanman, & Shekelle, 2016; Tricco et al., 2018).

At the beginning of the research, the research strategy was specified in a study protocol and coordinated with the German Environment Agency (UBA), the following key points were defined:

- key criteria (e.g., **P**opulation, **I**ntervention, **C**ontrol, **O**utcome (PICO))
- search areas (databases, Google etc.)
- search terms and strings
- inclusion and exclusion criteria (time, country und language of publication, type of publication and access)
- protocol for documentation, tables, and data extraction
- review-team, time and work plan, tools.

2.1 Search strategy

Four searches for the above-mentioned terms were performed, considering synonyms in search 3 and 4 (see Table 1). Searches 1 and 2 were intended to analyse the use of the terms "negligible" and "no exposure" in a broader sense, and therefore were performed in the multidisciplinary database Scopus, in Google and in legal databases. Searches 3 and 4 were not carried out in Google and LawInsider since neither platform can process comprehensive search strings.

Table 1: Search terms and searches

Search No.	Term	Search terms/ Synonyms	Search fields	Search areas
Search 1	negligible	negligible	Title	Scopus, Google, EuroLex, LawInsider

Search No.	Term	Search terms/ Synonyms	Search fields	Search areas
Search 2	"no exposure"	„no exposure" „not any exposure"	Title:~1*	Scopus, Google, EuroLex, LawInsider
Search 3	"negligible exposure"	"negligible exposure"	Title	All databases (Table 3) except LawInsider, Google
		"negligible exposure"	Title/ Abstract	"
		negligible AND exposure	Title	"
		insignificant AND exposure	Title	"
		irrelevant AND exposure	Title	"
		accessory AND exposure	Title	"
		marginal AND exposure	Title	"
		minor AND exposure	Title	"
		null AND exposure	Title	"
Search 4	"negligible concentration"	"negligible concentration"	Title	All databases (Table 3) except LawInsider, Google
		"negligible concentration"	Title/ Abstract	"
		negligible AND concentration	Title	"
		insignificant AND concentration	Title	"
		irrelevant AND concentration	Title	"
		accessory AND concentration	Title	"
		marginal AND concentration	Title	"
		minor AND concentration	Title	"
		null AND concentration	Title	"

* ~1: maximal 1 word may appear between both search terms

In addition, three search runs for definitions of the term "closed system" were performed using only the advanced Google search (search terms: "pesticide closed system", "plant protection closed system", "greenhouse pesticide closed system").

The search was restricted (see Table 2):

- to subject areas of life sciences
- to publications that appeared in the year 2010 or later
- to English-language publications
- to primary, secondary and grey literature
- to publications whose full texts are available.

Table 2: Inclusion and exclusion criteria

Criterion	Inclusion	Exclusion
Subject area	life sciences: human, animal and plant health, environment, food, pharmacology, earth science, research	chemistry, computer science, cryptography, economics, engineering, genetics, linguistics, modelling, physics/ chemistry, physics, psychology, social science, statistics
Year of publication	2010 or later	before 2010
Language	English	other languages
Country of publication	no restrictions	-
Type of publication	primary literature (studies); secondary literature (reviews) grey literature (project, authority reports) term definitions (dictionaries)	conference contributions interviews press reports editorials
Access	full text accessible	no full text available

2.2 Search areas

A comprehensive literature search was conducted in English in electronic literature databases with a scientific or legal focus (see Table 3).

Table 3: Search areas

Database	Web address
PubMed	https://pubmed.ncbi.nlm.nih.gov/
Scopus	https://www.scopus.com/home.uri
Web of Science (WoS)	https://login.webofknowledge.com
CAB Direct (CAB)	https://www.cabdirect.org/cabdirect
LIVIVO	https://www.livivo.de/
LawInsider	https://www.lawinsider.com/
EUR-Lex	https://eur-lex.europa.eu/

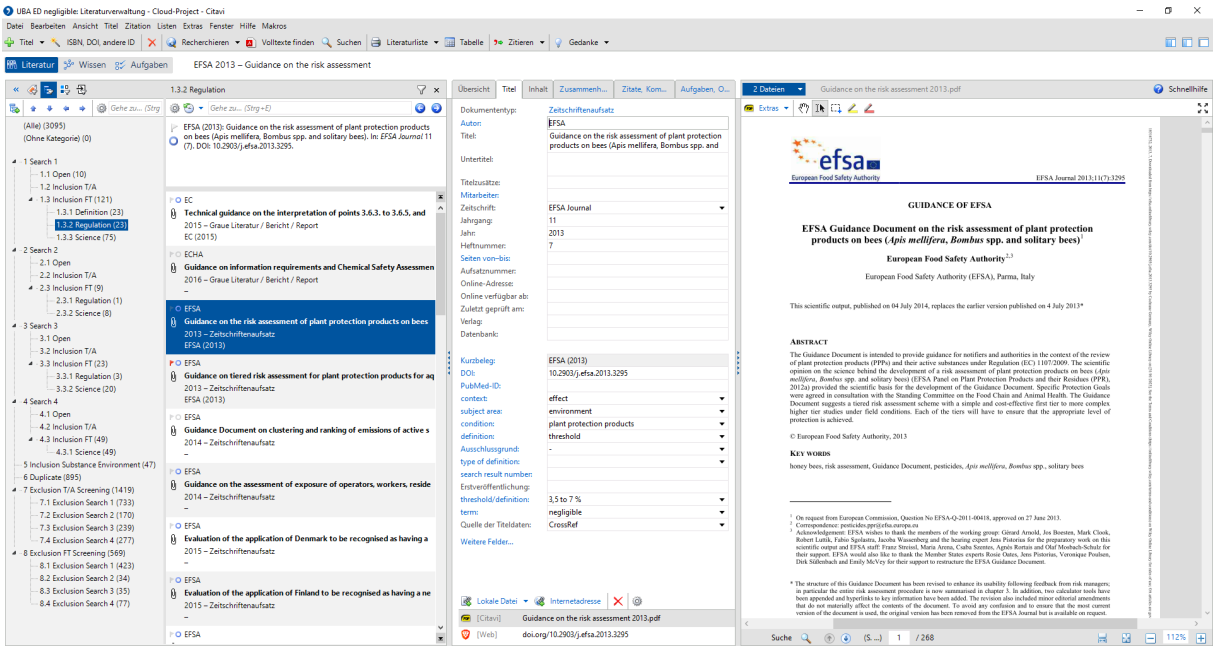
Searching for grey literature was done using the advanced Google search (according to BioMath standard operating procedure). All viewable results were considered.

A backward reference search with key publications was performed manually after searching literature databases and searching for grey literature.

2.3 Reference management

The search results were stored and categorised in a reference management software (Citavi 6, © 2020 Swiss Academic Software GmbH) project, specifying the source (search area), type of publication, online address, and bibliographic information (author(s), title, journal, year, volume, DOI, etc.). The search results from different databases or other search areas were merged and duplicates were removed (see Figure 1).

Figure 1: Reference management



Source: own illustration, BioMath GmbH

2.4 Study selection

Articles were selected in two steps: First, the titles and abstracts of the identified publications were screened (i.e., Title/Abstract (T/A)-screening) primarily against the inclusion criteria and the exclusions were documented. Then, the full texts of the manuscripts were screened (i.e., Full text (FT)-screening). The selection was based firstly on the defined key criteria (see Table 2) and secondly on the suitability of the studies. This concerned the presentation and comprehensibility of the definition of the term "negligible".

The selection process was illustrated shown in a flow chart according to PRISMA[1] (Liberati et al., 2009; Moher, Liberati, Tetzlaff, & Altman, 2009; Page et al., 2021).

2.5 Data extraction

During the extraction process, various elements were collected from the selected publications. These elements comprised:

- The condition, pertaining to the presence and identity of any specific substance.

[1] Preferred Reporting Items for Systematic reviews and Meta-Analyses

- The context, i.e., concentration, exposure, or effect (see 3.3.2).
- The method (e.g., threshold, limit of detection)
- The subject area (e.g., environment, human health, chemistry, and social sciences).
- The type of definition, i.e., narrative, qualitative, or quantitative (see 3.3).

So that ultimately all this helps systematically to definitions and interpretations of the terms "negligible", "no exposure", "negligible exposure", or "negligible concentration".

2.6 Synopsis of the search results and reference to chemicals

A structured synopsis was formed based on the definitions and interpretations of the terms "negligible", "no exposure", "negligible exposure", and "negligible concentration". The synopsis structure was primarily guided by context. Certain publications were individually identified as key publications due to their unique importance.

The extraction process focused on detailing the methods used for defining negligibility, such as threshold and limit of detection. Where applicable, the corresponding values or additional information associated with these methods were also compiled and documented.

2.7 Transferability and conclusions

Finally, a transferability of the definitions to environmental negligible exposure of endocrine disruptors was discussed.

3 Results

3.1 Search and selection process

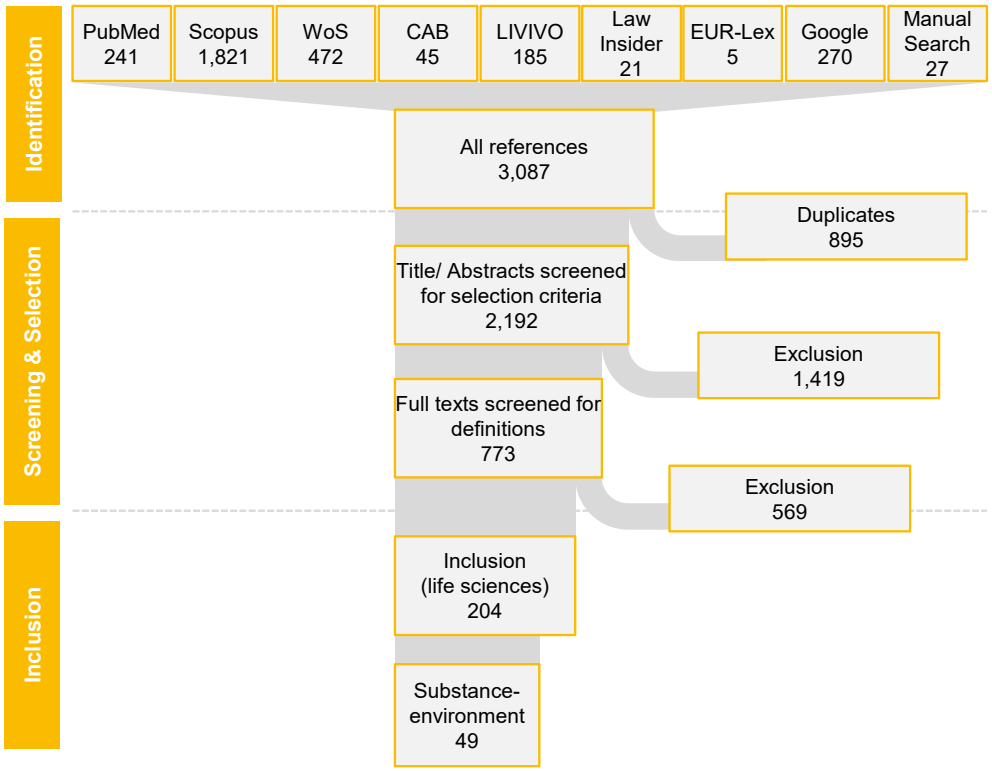
The search was conducted between April 3rd and 6th 2023. A total of 3,087 publications were identified in the four searches in all databases, the Google search, and the free search - this includes 27 publications found through manual searching (see Figure 2, and Figure 3).

Following the exclusion of duplicates (895) and the application of pre-defined protocol criteria, 2,192 titles and abstracts underwent screening. This process resulted in the exclusion of 1,419 publications based on the criteria outlined in Table 2, namely: publication type, year of publication (before 2010), language (other than English-language), and relevance of publication (context, meaning of the term, e.g. term "no exposure": "NO_2 exposure" (nitrogen dioxide exposure), "no exposure to banks/coins", term "minor": "common duckweed *lemna minor* exposed to", "arsenic exposure in minority, low-income, and indigenous populations").

During the T/A-screening, all publications were assigned to one of 21 different subject areas, including environment, human health, chemistry, and social sciences. Only those publications falling under the category of life sciences or those offering definitions from dictionaries were deemed relevant and thus included. All other publications were excluded due to their lower relevance (see Table 2).

The FT-screening process further eliminated 569 publications, leaving 204 publications from life science subject areas to be included. Out of these, 49 publications described negligible exposure of (chemical) substances to the environment (substance-environment subgroup).

Figure 2: Flowchart of the search and selection process

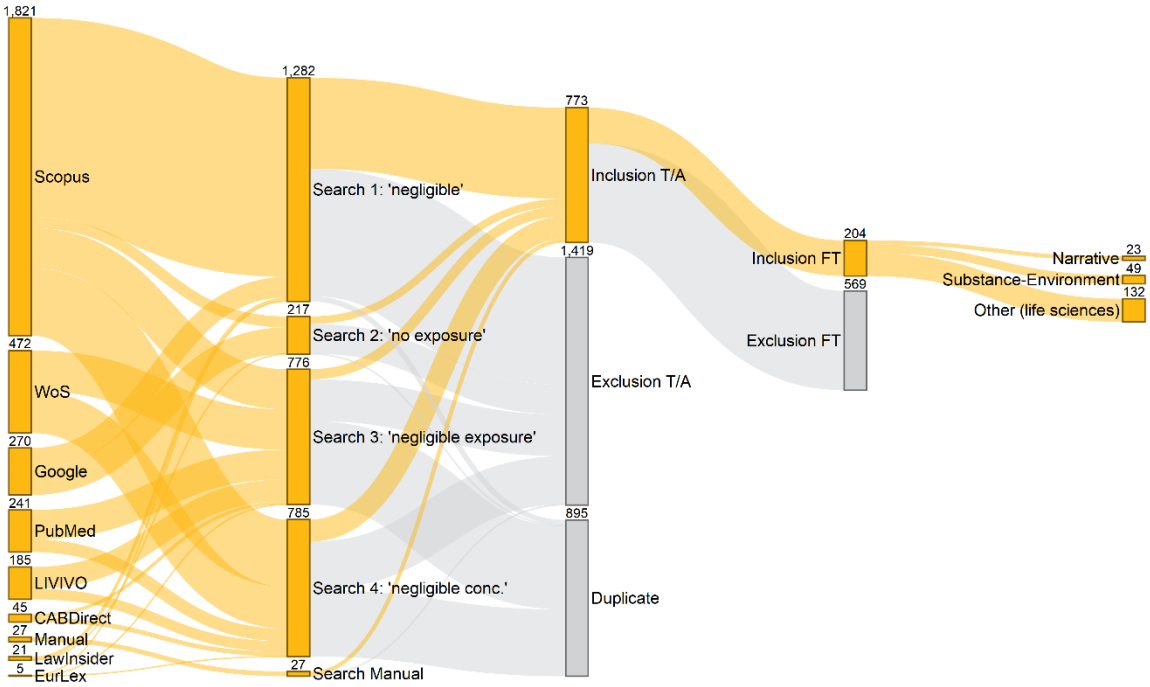


Source: own illustration, BioMath GmbH

3.2 Search results and study characterisation

Most publications (1,282 out of 3,087) were identified via search 1 using the single search term "negligible" (Figure 3). While it is to be expected that more general search 1 returns the most hits, it should be noted that because searches 1 through 4 were conducted in sequence (with 1 first and 4 last), any duplicates found between searches were usually attributed to the later search. This chronological allocation of duplicates contributes to the seemingly higher number of successful selected publications from search 1, which may cause misinterpretation of the findings.

Figure 3: Sankey plot of the search and selection process



Source: own illustration, BioMath GmbH

The largest proportion of the 204 included publications (from life sciences) was assigned to the subject areas environment (64) and human health (57) (see Table 4).

Table 4: Subject areas of included publications

Category	Subject area	Number of included publications
life sciences	environment	64
	human health	57
	food	18
	pharmacology	16
	animal health	14
	plant health	9

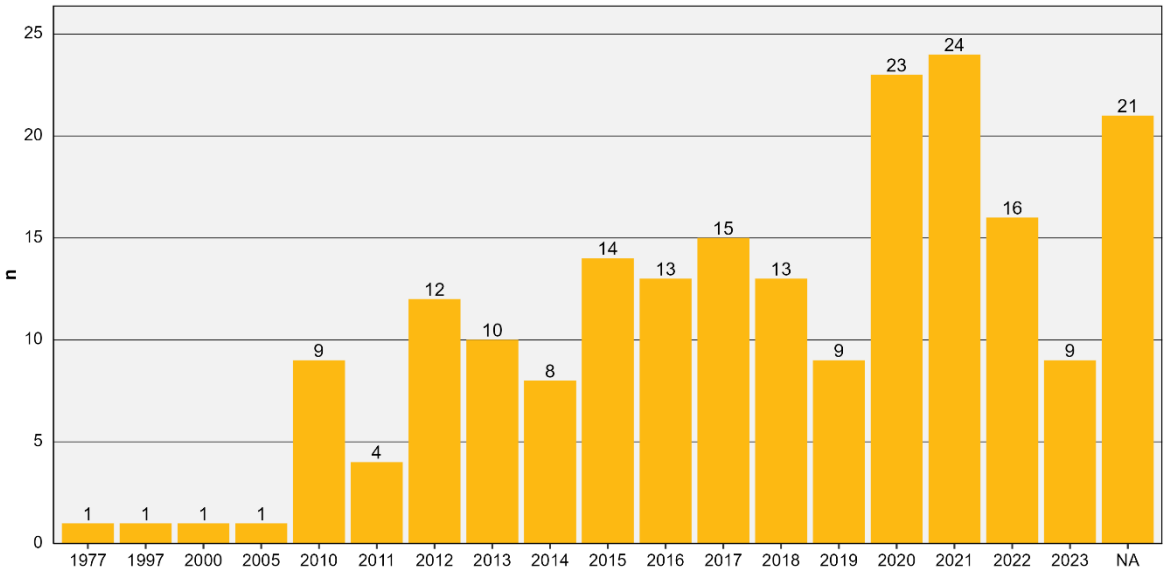
Category	Subject area	Number of included publications
	earth science	3
neutral	dictionary	23
	Total	**204**

Source: own illustration, BioMath GmbH

In accordance with the exclusion criteria provided in Table 2, all the incorporated publications were disseminated between the years 2010 and 2023 (cut-off-date 6th April 2023) (see Figure 4). However, four publications from the manual search with publication dates before 2010 were also included due to their substantial relevance. These consist of two publications from the Environmental Protection Agency (EPA) – the "Interim Guidance on Control of Volatile Organic Compounds in Ozone State Implementation Plans" (EPA, 2005) and the "Recommended Policy on Control of Volatile Organic Compounds" EPA (1977), and the two scientific publications from Kalf, Crommentuijn, and van de Plassche (1997) and Crommentuijn, Sijm, Bruijn, van Leeuwen, and van de Plassche (2000). The bulk of the publications originate from the years 2021 and 2020. Note that all publications where the year of publication is not available are dictionary entries.

Figure 4: Number of included publications per publication year

For 2023, only papers published until the last search date (April 6th, 2023) are included. Publications where the year of publication is not available are web dictionaries.



Source: own illustration, BioMath GmbH

Upon further analysis, the final selection of 204 publications underwent additional categorisation, such as their type (narrative, qualitative and quantitative; see 3.3), their concept (concentration, exposure, effect; see 3.3.2) and whether their definition of "negligible" was in relation to a (chemical) substance.

The latter was executed to delineate an even more relevant subset of included publications that addressed substances within the subject area of "environment". From the total of 204, there are

49 publications that fit into this substance-environment subgroup. These publications have been thoroughly examined in the subsequent sections of this report. Yet, tables with all 204 publications and their extracted categories as well as a short description can be found in the appendix.

3.3 Synopsis of definitions of the terms in the literature

This chapter presents a comprehensive examination of the uses and interpretations of the terms "negligible", "no exposure"[2], "negligible exposure", and "negligible concentration" across various disciplines. While we have labelled them as "definitions" for ease of reference, it should be clarified that these often represent specific applications or interpretations of the terms, rather than entirely new definitions. These interpretations have been grouped into three types:

- **Narrative definitions** describe or paraphrase the meaning of a term (e.g., using synonyms). This type of definition is typically found in dictionaries and in fact all narrative definitions in this project have been extracted from dictionaries.
  Example: The effect on the heart is negligible if it is of very little importance and not worth considering.
- **Qualitative definitions** list specific criteria that must be met to classify something as negligible or qualitatively state "no" or "very low" or "not observed" or similar.
  Example: The effect on the heart is negligible if the heart rate is not affected.
- **Quantitative definitions** define the term using a numerical value or a range, such as a threshold to be undercut, a value to be met, a probability to be undercut or a range to fall within.
  Example: The effect on the heart is negligible if the heart rate does not change by more than 10%.

It's worth noting that in both regulatory and scientific domains, these types of definitions are ranked, in terms of their precision and applicability, as follows: narrative < qualitative < quantitative. It can be further argued that a definition from any one of these categories can, in principle, be translated into one from another category. However, such conversion can lead to the loss or necessity of additional information. For instance, transitioning from a quantitative to a qualitative definition often results in the loss of explicit numerical thresholds or similar parameters (as exemplified above). Conversely, upgrading a definition—such as converting from a narrative to a qualitative definition, or from a qualitative to a quantitative one—requires additional specifications. Simply put, it involves addressing the question, "What does this mean exactly?" and is the driving force behind. For instance, the conversion from a narrative to a qualitative definition might require identification of specific reference traits, while the transition from a qualitative to a quantitative definition typically involves determining a specific numerical threshold. The following statement of the European Food Safety Authority (EFSA) in EFSA Working Group for the revision of the bee guidance (2020) highlights the significance of using quantitative instead of qualitative definitions: "The EFSA Scientific Committee (2016) suggests avoiding using the terms 'negligible', 'small', 'medium', 'large' as descriptors of the magnitude of effects because these terms can be considered vague and qualitative".

Most of the 204 included publications belong to the quantitative group (see Table 5).

[2] For the term "no exposure" only few definitions were found, either narratively stating "no exposure" to be negligible or quantitatively defining a threshold for "no exposure". In the following, the definitions of this term therefore are pooled with the definitions of "negligible exposure".

Table 5: Types of definitions identified in the included publications

Type	Number of included publications (life sciences)
narrative	23
qualitative	32
quantitative	149

In the following sections, narrative definitions are summarized first, followed by a joined synopsis of all qualitative and quantitative definitions.

3.3.1 Narrative definitions: paraphrasing the term „negligible"

Our comprehensive review of 23 dictionary entries revealed that the term "negligible" signifies something so small, unimportant, or insignificant that it becomes inconsequential and can safely be neglected or disregarded (see Table 6). This spans across a spectrum of contexts, whether that be in terms of size, importance, or even potential effects. The definitions can be grouped into two major themes:

- Lack of Worth or Insignificance: Most of the sources interpret "negligible" as referring to an element so trivial, small, or unimportant that it's not worth considering. This category encompasses definitions of being safely disregarded or ignored, being meaningless, not warranting attention, and being of no importance. Some of the specific descriptors used include "trifling", "insignificant", "not worth considering", "unworthy of notice", "of no account", and "contemptibly unimportant".
- Quantitative Minutia: Some sources spotlight the term's use in quantifying the extent or probability of something, particularly when that measure is minimal. This group includes definitions such as "small in degree, especially of probability", and "of very little importance or size".

In summary, "negligible" uniformly points to something so small, insignificant, or unimportant that it lacks worth and can be overlooked or disregarded across various contexts and perspectives.

Table 6: Paraphrasing of the term „negligible" in dictionaries

Description	Number	Sources
so small/ unimportant/ trifling as not to be worth considering/ worrying about	9	Collins Wörterbuch, 2023; Forvo Academy, 2023; Oxford English Dictionary; TheFreeDictionary.com, 2023; Vocabulary.com, 2023; Wordpandit, 2012; WordReference.com, 2023; World Law Dictionary, 2023; YourDictionary, 2023
so small/ unimportant/ trifling as to be (safely) disregarded, ignored, or neglected	4	Online Etymology Dictionary, 2023; Oxford English Dictionary; Simple English Wiktionary, 2023; WordReference.com, 2023
so small/ unimportant/ trifling as to be meaningless	4	Antonym.com, 2023; sentencedict.com, 2023; TheFreeDictionary.com, 2023; Vocabulary.com, 2023

Description	Number	Sources
so small/ unimportant/ trifling as to warrant little or no attention	1	Merriam-Webster, 2023
so small/ unimportant/ trifling that it has no significance	1	YourDictionary, 2023
insignificant	8	Antonym.com, 2023; Forvo Academy, 2023; Myefe, 2023; Oxford English Dictionary; sentencedict.com, 2023; TheFreeDictionary.com, 2023; Vocabulary.com, 2023; WordReference.com, 2023
not worth considering	5	Myefe, 2023; Oxford Advanced Learner's Dictionary, 2023; Oxford English Dictionary; sentencedict.com, 2023
(very) unimportant or small	4	Macmillan Dictionary, 2023; Macmillan Thesaurus, 2023; Simple English Wiktionary, 2023; The Britannica Dictionary, 2023
able to be neglected or disregarded	1	Oxford English Dictionary
not significant or important enough to be worth considering	2	TheFreeDictionary.com, 2023; YourDictionary, 2023
trifling	4	Dictionary.com, 2023; TheFreeDictionary.com, 2023; WordReference.com, 2023; YourDictionary, 2023
nominal	1	Merriam-Webster, 2023
not eligible	1	Wordpandit, 2012
of little worth, substance, or significance	1	Oxford English Dictionary
of no account	1	Oxford English Dictionary
of very little importance or size	1	Oxford Advanced Learner's Dictionary, 2023
small in degree, especially of probability	1	TheFreeDictionary.com, 2023
too slight or small in amount to be of importance	1	Cambridge English Dictionary, 2023
unworthy of notice or regard	1	Oxford English Dictionary

3.3.2 Qualitative and quantitative definition of "negligible exposure"

3.3.2.1 Interrelation of "exposure", "concentration" and "effect", and crucial level definitions

Throughout the process of gathering and summarizing all definitions for negligible exposure, it was evident that the general term "exposure" is interrelated with the concentration of a substance, on one hand, and the potential effects that the substance can cause, on the other. So, by referring to "negligible exposure" also "negligible concentration" as well as "negligible effects" were described. Based on the knowledge accrued during the investigation of this project, the concepts of concentration, exposure, and effect were succinctly developed as follows:

- **Concentration**: This term refers to the quantity of a substance, such as an endocrine disruptor, present in a specific environmental medium (air, water, soil, etc.). Strictly speaking, the concentration alone does not dictate risk or impact on health and ecosystems. It is merely a static measurement, providing no direct information on the actual interaction between the substance and living organisms or the environment. A concentration threshold might thus be perceived as the minimum level of a substance leading to an exposure that precipitates a particular effect.
- **Exposure**: This captures the actual level of a substance that an organism encounters, considering frequency and duration of contact, route of exposure (e.g., ingestion, inhalation), and the behaviour and characteristics of the organism itself. It signifies the level of substance the organism has the potential to encounter. In practical applications, distinguishing between the „concentration" of a substance in the environment and the „exposure" of an organism to that substance often poses challenges, as the means of accurately measuring these two distinct quantities are not always clear or feasible. An exposure threshold might be defined as the minimum exposure level to a substance that precipitates a particular effect. Finally note, that due to absorption, distribution, metabolism, and excretion (ADME) processes in an organism the release of a substance to the environment may result in multiple metabolites, each with separate effects within the exposed organism.
- **Effect**: This is the biological change or outcome that results from the exposure to a substance. The Effect ties together both Concentration and Exposure. An effect threshold could be defined as the smallest detectable level of biological change or response that is seen as relevant, essentially viewed as "a particular effect" in the above thresholds.

Following the explanation of these fundamental concepts, a set of crucial terms within this domain can be considered. Each term holds its own value but is also intricately interconnected with the concepts of concentration, exposure, and effect:

- Limit of Detection (LOD) and Limit of Quantification (LOQ): Defined as the smallest quantities of a substance that can be reliably detected and quantified, respectively (Geldsetzer, 2023a, 2023b).
- Predicted Environmental Concentration (PEC): An estimation of the level of a substance in the environment that an organism is expected to encounter (RÖMPP-Redaktion, 2023).
- No Observed Adverse Effect Level (NOAEL) and Lowest Observed Adverse Effect Level (LOAEL): They denote the exposure levels of no observed effect concentration (NOEC) and the lowest observed effect concentration (LOEC) that have not led to noticeable adverse effects or have produced the smallest observed adverse effects derived from chronic toxicity test, respectively (Wagner-Roth, 2023a, 2023b; Wagner-Roth & Hofer, 2023).
- Median effect concentration (EC_{50}): mostly derived from acute toxicity test pointing to a deleterious effect in 50% of the experimental population. One example is the median lethal concentration (LC_{50}), where half of the experimental population dies. (RÖMPP-Redaktion & Wagner-Roth, 2023a, 2023b)
- Predicted No-Effect Concentration (PNEC): PNEC is an exposure level below which the substance is not anticipated to inflict harm. PNEC values are derived from LOEC values and PNEC calculations are carried out using together assessment factors or statistical extrapolation techniques to address uncertainties (Berger, 2023).

- Regulatory Acceptable Concentrations (RAC) and Environmental Quality Standards (EQS): prescribe a specific concentration level in the environment beyond which the substance may cause potential harm, determined from ecotoxicological data which were evaluated within the framework of the authorization procedure (Pflaumbaum & Geldsetzer, 2023).
- Benchmark Dose (BMD) and Benchmark Risk (BMR): represent an exposure estimate associated with a certain level of risk or effect size. e.g., BMR_{10} corresponding to the BMD_{10} that induces a response in 10% of experimental specimens (Habermeyer, 2023).
- Exposure toxicity ratio (ETR): the ratio between exposure (usually the concentration in a certain environmental compartment) and toxicity for relevant organisms (Feola, Rahn, & Binder, 2011)

Despite each term possessing a unique definition and typically describing a concentration or level, it is impossible to categorically link these terms to one of the concepts of concentration, exposure, or effect exclusively, given their interconnected nature. It is, however, noteworthy that the determination of most of these terms fundamentally hinges on the resultant effect.

3.3.2.2 "Negligible" environmental concentration, exposure, or effect of (chemical) substances

The ensuing section presents an overview of the findings from the 49 publications comprising the substance-environment subgroup. It has been structured to first summarize findings separately for concentration, exposure, and effect, before highlighting key publications individually.

Concentration

In most publications, concentrations were deemed negligible simply because the values were extremely low. However, these studies did not provide a defined threshold or cutoff point to specify the exact magnitude that constituted this "extremely low" measurement (Braeckevelt, Seeger, Paschke, Kuschk, & Kaestner, 2011; Häggi et al., 2021; Humez et al., 2016; Kandji, Plante, Bussière, Beaudoin, & Dupont, 2017). As an exceptional case, Olarieta, Rodríguez-Ochoa, Ascaso, and Antúnez (2016) set a fixed threshold of 30 mg/g for negligible gypsum concentrations in the surface mineral horizon, although the specific basis for this value remains unclarified. Inversely, Decesari et al. (2010) describe a concentration of 0.36 µg/scm elemental carbon in PM_{10} fraction to be non-negligible.

Several publications considered a concentration negligible if the measured values fell below the LOD (Burducea et al., 2022; Davenport, Bair, & Stevens, 2012; Khan, Li, Zhang, & Malik, 2016). This method is straightforward, but it must be considered within the context of the state of the art at the publication date since technological advancements in analytical methods lead to a decrease in LODs with time.

In four cases, all related to the concentration of heavy metals in soil or water (Burducea et al., 2022; Prapagdee & Khonsue, 2015; Rosyida, Suranto, Masykuri, & Margono, 2022; Singh, Vashistha, Chandra, & Rai, 2021), negligibility was equated with being below a legal threshold (e.g., set by a national ministry, standard, EPA, or World Health Organization - WHO). The approach of Sigua, Hubbard, and Coleman (2010) can be seen as somewhat similar, though they based their threshold for negligibility (in relation to phosphorus concentration in soil) not on a legal threshold, but one that had been published in other peer-reviewed literature.

Interestingly, there were three publications examining the concentration of polycyclic aromatic hydrocarbons in riverbeds (Dauner et al., 2018; R. Li et al., 2019; Zhang et al., 2018) that all employed a method published by Kalf et al. (1997), to estimate the "Risk Quotient of Negligible

Concentrations (RQ_{NCs})". According to this approach, a potential ecological risk is deemed negligible if the RQ_{NCs} is less than 1. To obtain this measure, they first establish the Maximum Permissible Concentrations (MPCs). The MPCs are extrapolated from ecotoxicological data using empirical evidence or, when insufficient data is available, using Quantitative Structure-Activity Relationship models (QSARs). The calculated MPCs are then harmonized across environmental compartments using equilibrium partitioning methods or multimedia fate models. After defining the MPCs, Negligible Concentrations (NCs) are then simply computed as the MPC divided by 100[3], thereby accounting for potential combination of toxic effects. Crommentuijn et al. (2000) also described methods to estimate MPCs and NCs and derived them for water, sediment, and soil for approximately 150 organic substances and pesticides. MPC is the concentration in the environment above which the risk of adverse effects was considered unacceptable to ecosystems. Again, the NC is defined as 1% of the MPC without further information why specifically this value was chosen.

Exposure

Just like for concentration, the exposure in several studies was determined to be negligible due to its small size, yet a specific cutoff value was not provided to gauge what might qualify as "small" (Bergman & Bump, 2014; Guidi, Degl'Innocenti, Carmassi, Massa, & Pardossi, 2011; Massar, Dey, Barua, & Dutta, 2012; Sundberg & Karvonen, 2018).

Shams et al. (2010) serve as another instance of this approach, with a slight variation: The assessment of negligibility appears to be based not solely on the absolute concentration being small, but also on its relative size when compared to the concentrations in other crops from the same experiment, following the exposure of multiple crops to different levels of chromium contamination.

Beiras and Schönemann (2020) initially identified a „safe concentration" threshold of 13.8 mg/L for exposure to microplastics, subsequently estimating the risk of marine organisms encountering a concentration higher than this threshold. The assessed risk was found to be 0.00004, and was "therefore […] negligible", i.e., also considered small without providing an explicit cutoff value upon which this decision is based.

An instance of legal threshold application is seen in the work of Santis et al. (2021), who identified mycotoxin contamination in groundnut as negligible due to its measurements falling "below the maximum levels tolerated by international standards" (specifically, Ugandan Standard East African Standard 57-1 on groundnut).

Effect

A source that recognized a very low value for determining negligibility was Powell (2013). Here, the 2010 World Trade Organization (WTO) Australia – Apples Panel posits that risks can be effectively viewed as negligible if event probabilities fall within a specific triangular distribution model where the most probable value is zero and the maximum value is 10^{-6}. This model is proposed to be more accurate than a uniform distribution model, thereby offering a concrete, quantifiable interpretation for a "negligible" probability. In less technical terms, the panel suggests interpreting "negligible risk" if the probability of an event is lower than one in a million. Note that this particular numerical value, 1/1,000,000, also appears in some of the other 204 included publications: As an example, Alban and Petersen (2016) applied the value 1/1,000,000 in assessing biosecurity risks in pig farming, using this figure to denote the low likelihood of *Trichinella* presence in an indoor compartment. Similarly, in a study assessing health risks from

[3] The NC is simply defined as 1% of the MPC.

chemical emissions, D. Li and Li (2021) noted that the highest health risk, specifically a three-year-old's exposure to acrolein, was still negligible, calculated as less than one in a million.

Five studies were discovered that investigated the mean effects of an exposure on an organism and compared these to a control group lacking the exposure. The effect differences were deemed negligible if the p-value of a statistical test for the comparison was not statistically significant, i.e., ≥0.05 (Fabre et al., 2020; Payne, Walsh, & Rangel, 2019; Qiang, Lo, Gao, & Cheng, 2020; Scopetani, Esterhuizen, Cincinelli, & Pflugmacher, 2020; Xu et al., 2020).

Three studies employed benchmarks for comparison: Govindarajan, Hoti, Rajeswary, and Benelli (2016) determined the toxicity against larvae of NTOs as negligible if mortality did not increase until 48 hours after exposure to 50 times the median lethal dose (LC_{50}) for target organisms. Long, Guan, Kanemoto, and Gasparatos (2021) considered an effect (carbon footprint of households) during a recent exposure event negligible as it was comparable to the effect in the period preceding the event. The definition of EPA (1977) provides a quantitative and pragmatic benchmark: The United States Environmental Protection Agency (EPA) and States exclude certain "negligibly" reactive compounds from the regulatory definition of volatile organic compounds, exempting them from regulation as ozone precursors. This exemption gives industry an incentive to replace higher reactivity compounds with negligibly reactive ones and to invest in the development of negligibly reactive compounds and low reactivity formulations (EPA, 2005). Since 1977, EPA has used the reactivity of ethane as the threshold for a negligible reactivity (effect). Compounds that are less reactive than or equally reactive to ethane have been deemed negligibly reactive. EPA believes that ethane continues to be an appropriate threshold for defining negligible reactivity and that a comparison to ethane on a mass basis strikes the right balance between a threshold that is low enough to capture compounds that significantly affect ozone concentrations and a threshold that is high enough to exempt some compounds that may usefully substitute for more highly reactive compounds (EPA, 2005).

Notably, EFSA (2013b, p. 249) in one case finds "potential risks to aquatic organisms of exposure to [a fungicide]" to be "likely negligible" because PEC is lower than the RAC. Moreover, EFSA (2022c) define a negligible effect as "no increase in the frequency or magnitude of mortality and visual suffering between exposed and unexposed groups".

Lastly, two publications primarily deemed the investigated effects of an exposure negligible in comparison to the more substantial effects of a secondary exposure they also studied. Herzke et al. (2016) suggested that the effect (persistent organic pollutants in tissue) of an exposure (ingestion of plastic) is negligible as the effect of another exposure (ingestion of natural prey) is more significant. Furthermore, when Greenslade, Reid, and Packer (2010) compared effects (abundance of ants and springtails) with and without exposure (herbicide applied to a wheat field), they labelled the exposure as negligible - even though the difference was statistically significant ($p < 0.05$) – due to the noticeably larger effect of the exposure to a second factor (tillage) in their experiment.

Key Publications

A paper that directly discusses negligible exposure of endocrine disruptors is "Refinement of the ECETOC approach to identify ED properties of chemicals in ecotoxicology" as published by Weltje, Wheeler, Weyers, and Galay-Burgos (2013). It expands on the research conducted by the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) task force, seeking to establish scientific criteria within these legislative structures.

In this paper negligibility is implied to lie somewhere between zero and a regulatory acceptable concentration as determined through an appropriate risk assessment. Therefore, negligible exposure only can be defined for chemicals where there is agreement on a toxicological threshold for endocrine-mediated adverse effects, and where no adverse effects are expected below this threshold. The authors are of the opinion that such toxicological threshold values exist, and advise against setting a fixed, arbitrary concentration - comparable to the groundwater cutoff value of 0.1 µg/L - as negligible, pushing instead for a science-based approach that takes both hazard and exposure into account.

Three EFSA sources that offer significant insights are the "EFSA Guidance Document on the risk assessment of plant protection products on bees" (EFSA, 2013a), the "Review of the Guidance Document for the risk assessment for bees" (EFSA Working Group for the revision of the bee guidance, 2020), and the "Revised guidance on the risk assessment of plant protection products on bees (*Apis mellifera, Bombus spp*. and solitary bees)" (EFSA, 2023c). Here, several approaches defining specifically what constitutes "negligible" exposure/effects are introduced:

- Regarding bees' risk from exposure to guttation water it is suggested to count the number of location-year combinations where guttation occurs. If it is <10% of the total, "exposure is considered negligible" (EFSA, 2013a, p. 43).
- An exposure is considered negligible if its 90th percentile does not exceed the NOEL. The assessment relies on the computation of the ratio of exposure and toxicity ratios and the application rate evaluated against predefined trigger values (EFSA, 2013a, p. 85).
- An effect is considered negligible when the reduction in the size of a honey bee colony falls between 3.5% and 7%, offering a metric that works in concert with the established ETR and trigger value system for evaluating exposure levels (EFSA, 2013a, p. 98).
- An exposure is deemed negligible if the daily mortality increases no more than 1.5 times relative to the control for a period of six days, whilst taking into account ETR calculations and corresponding trigger values (EFSA, 2013a, p. 101).
- In the 2023 published guidance the exposure scenarios were reviewed and the methodologies for exposure and hazard assessment of the previous EFSA Guidance Document (2013a) were updated. In principle, an effect of pesticides smaller than the normal variability within and between unexposed colonies is now considered negligible. In contrast to the first approach from 2013, the value of 10% was used instead of 7%, i.e., if the difference in the sublethal effects between treatment and control is ≤ 10%, it is assumed that even in the worst case, the reduction in colony size will be unlikely to breach the specific protection goals of bees.

Note that specifically the latter notions are similar to how "negligible effects on birds and mammals typical for agricultural landscapes" are regarded within the "Risk assessment for Birds and Mammals" (EFSA, 2023d). Here, a negligible effect is defined as one not exceeding the response of the assessment endpoint under non-exposed field conditions within a relevant time period.

Then there is a discussion in EFSA Working Group for the revision of the bee guidance (2020) about the term "negligible" and its potential limitations. As mentioned before, the EFSA Scientific Committee suggests that terms like "negligible", "small", "medium", and "large" can be considered vague and qualitative. They express that these terms can create disagreement when they are quantified, as they are not rooted in clear biological thresholds. Therefore, as part of the proposed approach, the term "threshold of acceptable effects" is introduced. This is seen as a more

suitable term because it accounts for the expected background variability of colony sizes. With this approach, the level of effect following pesticide exposure should always remain within this acceptable range. However, the publication does not expressly suggest to entirely revoke the term "negligible" and replace it with "acceptable". Instead, it proposes a new way to establish an "acceptable" threshold for effects based on the variability in colony sizes. This "acceptable" threshold is to be used when assessing the effects of pesticides on bee colonies, which could be seen as a more specific and scientifically based alternative to vague qualitative terms such as "negligible".

Considerations on whether the exposure can be considered negligible were concluded by EFSA during the peer review of the pesticide risk assessment of the active substances benthiavalicarb-isopropyl, clofentezine, asulam-sodium, dimethomorph, metiram and triflusulfuron-methyl, which were considered endocrine disruptors in result of the assessment (EFSA, 2021a, 2021b, 2021c, 2022a, 2023a, 2023b). Negligible endocrine-disrupting properties of clofentezine, benthiavalicarb-isopropyl, and asulam-sodium for non-target organisms according to point 3.8.2 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605 could not be concluded based on the available data. The environmental exposure was concluded to be non-negligible for triflusulfuron-methyl, dimethomorph and metiram as the available PEC in soil, surface water and sediment for all the representative uses assessed are above levels that can be routinely measured. Furthermore, it was stated that there will be exposure to triflusulfuron-methyl, dimethomorph and metiram via food items of non-target organisms for the representative field uses, as these organisms will enter fields on the same day an application is made.

4 Transferability of results

It is obvious that both narrative and qualitative definitions should be avoided because these terms can be considered vague and not resilient. If possible, a quantitative definition should be applied. Such quantitative definition of negligible exposure corresponds to a risk-based approach which places emphasis on assessing and managing the risks of the chemical in use and keeping possible exposure below thresholds (for instance through exposure mitigation). Nevertheless, such a definition is implementable only for endocrine active substances and species where hazard, exposure as well as MoA are known, and test methods are available. Moreover, negligible exposure can only be defined for chemicals where there is agreement on a toxicological threshold for endocrine-mediated adverse effects (Weltje et al., 2013).

When hazard, exposure and/or MoA are not known, or when validated test methods are unavailable, agreement on toxicological thresholds for endocrine-mediated adverse effects cannot be reached. In such cases, negligible exposure can only be described narratively – indicating an exposure close to zero – and is ensured only by minimising or excluding contact. Thus, emphasis is placed on limiting the exposure by using active substances in closed or by targeted systems, which corresponds to a hazard-based approach.

Transferability of identified definitions to the negligibility of environmental exposure to endocrine disruptors therefore connects to the identification and environmental risk assessment of endocrine active substances and their uncertainties.

4.1 "Negligible exposure" below threshold values

In a risk-based approach, "negligible" exposure can be defined quantitatively and corresponds to an exposure (or a concentration, an effect, respectively) below a threshold (e.g., LOD, NOAEL).

In fact, with respect to human health Regulation (EC) No 1107/2009, negligible dietary exposure is quantitatively defined as "where residues of the active substance, safener or synergist concerned in food and feed do not exceed the default value established in accordance with Article 18(1)(b) of Regulation (EC) No 396/2005". The default value is initially set to 0.01 mg/kg and shall not be exceeded, but it might be changed to the LOQ according to Article 18(1)(b) of Regulation (EC) No 396/2005. Non-dietary negligible exposure is further specified by EC (2015) to be assumed "where levels to which humans are exposed are equal to or lower than natural background levels in the environment, i.e. excluding background levels which have been increased during time by anthropogenic activities and/or which are considered to be a concern". For exposure assessment the Technical Guidance suggests in a 1st tier to follow the EFSA guidance (EFSA, 2014b) including, where applicable, the calculator developed by EFSA. For defining negligible exposure, an additional and protective "threshold" to the relevant toxicological reference value (e.g. AOEL) is set. As a 2nd tier, EC (2015) proposes to apply the Margin of Exposure to the study critical for the relevant classification for under Regulation (EC) No 1272/2008 and to set a sufficient safety margin (at least 1,000) for the purpose of demonstrating negligible exposure.

In its reviews of the risk assessment of endocrine active substances (e.g. EFSA (2021a), EFSA (2021b)) EFSA followed these procedures. Quantitative definitions of potential negligible exposure were also applied to non-target organisms except humans. E.g., PECs were applied to assess the risk of benthiavalicarb, dimethomorph, metiram or asulam-sodium to aquatic organisms (EFSA, 2021a, 2021c, 2023a, 2023b).

When defining exposure quantitatively, it should be considered that exposure of endocrine active substances can be mitigated to not exceed threshold levels through various strategies or measures, e.g. emerging digital technologies can minimise the use of PPP by e.g., automatically spraying only areas in need of treatment or spot spraying, forecasting models can avoid PPP treatments of pests where infestations are below damage thresholds, or spray shields can prevent harmful spray outs or leaks (targeted application) (Brown, Giles, Oliver, & Klassen, 2008; Rajmis, Karpinski, Pohl, Herrmann, & Kehlenbeck, 2022).

Nevertheless, as discussed by Weltje et al. (2013), Duis et al. (2014) and others, the intricate nature of environmental risk assessment of endocrine disruptors needs consideration of a range of crucial factors, when claiming for negligible exposure below thresholds. These include

- differential sensitivities across species,
- unclear toxic MoA,
- the availability of validated test procedures and guidelines,
- the significance, reproducibility and relevance of so-called "low-dose effects",
- nonmonotonic dose-response relationships and,
- the importance of understanding population-level effects.

Furthermore, and as stated before, it is important to consider that substances undergo ADME processes once taken up by organisms. Parent compounds may be metabolized into other compounds, leading to detoxification or even more toxic substances. Hence, for determining the effect, it's crucial to consider not only the environmental concentration/exposure of the parent compound but also knowledge about its metabolites and their formation rates.

4.2 "Negligible exposure" by minimising contact

In a hazard-based approach, "negligible" exposure corresponds to something so small, unimportant, or insignificant that it becomes inconsequential and can safely be neglected or disregarded – comparable to the narrative definitions of the term. For risk assessment purposes "negligible" can be considered as a level so small that it does not appreciably add to the risk and can safely be ignored (EC, 2015).

In fact, concerning human health, Regulation (EC) No 1107/2009 defines exposure as negligible when it is excluded, stipulating that "the product is used in closed systems or in other conditions excluding contact with humans". The legislation is not defining the terms "closed systems" and "excluding contact with humans". EC (2015) states that it is not possible to demonstrate "closed systems" throughout the entire life-cycle, but only to certain phases in the life of a PPP. For this reason, it defines closed systems to be "equipment and procedures designed to reduce as far as technically possible the escape of an active substance, safener or synergist into the environment either during or after the use of the plant protection product.". With regard to the environment and according to EFSA (2014a), permanent greenhouses with floors can be considered as nearly closed systems to the environment (emission via e.g. volatilization, condensation water, waste water can be limited), while for closed buildings defined as areas for post-harvest treatment with PPPs emission via air cannot be disregarded. However, exposure of NTOs to endocrine

disruptors in PPP could be considered negligible if applied in such closed places of crop production (subsequently called closed systems).

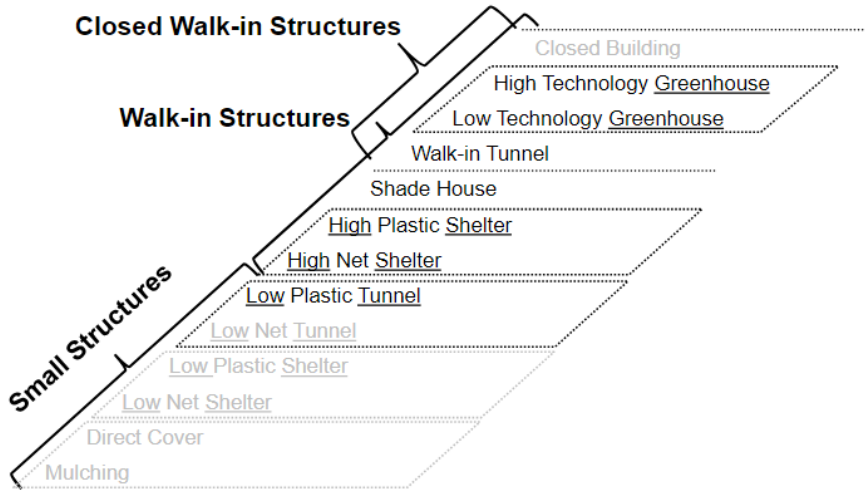
4.2.1 Closed places of crop production

Under EU regulation, protected crop systems (e.g., greenhouses and cultivations grown under cover) are considered as "closed systems" which prevent emission of PPPs post-application. Regulation EC/1107/2009 (EC, 2009) defines a greenhouse to be "a walk-in, static, closed place of crop production with a usually translucent outer shell, which allows controlled exchange of material and energy with the surroundings and prevents release of plant protection products into the environment".

Nevertheless, research reports and other sources suggest that emissions can still occur in such "closed" crop protection sites (EFSA, 2014a). Birds, mammals, non-target arthropods including bees and non-target plants may be exposed to and at risk from PPPs during and after their application to protected crops (EFSA, 2023d, p. 28 footnote 18; EFSA PPR Panel, 2014, 2015). Emissions from covered cropping systems might also occur because of removal of crop remnants, harvested products, substrates, and plastic materials. Consequently, EFSA prepared guidance on clustering and ranking of emissions of active substances of PPPs and transformation products of these active substances from protected crops (greenhouses and crops grown under cover) to relevant environmental compartments (EFSA, 2014a). EFSA developed a classification system for structures of closed places of crop production, categorising them into six major groups (see Figure 5): low (mini) tunnels, plastic shelters, net shelters, shade houses, walk-in tunnels, and greenhouses (low- and high-tech types); and proposed approaches for environmental exposure assessment for each of these structures. The isolation properties of these protected crop systems regarding emissions to different environmental compartments were assessed as follows:

- Soil: Concerning the soil compartment, all non-permanent structures (i.e., net/plastic tunnels/shelters, shade houses) are not considered "closed", and emission to this environmental compartment is comparable to open field.
- Groundwater: Regarding the groundwater compartment, all protection structures, excluding greenhouses with floors, are not considered "closed" as they may allow leaching to occur.
- Air: None of the structures is classified as "closed". However, closed buildings and greenhouses can be sealed with technical measures like air conditioning and filter systems.
- Surface water: All structures, except closed buildings and greenhouses, are not classified as "closed".

Figure 5: Main categories of "closed" places of crop protection



Source: EFSA (2010)

Regarding the penetration of NTOs, protected crop systems are deemed "closed" for organisms living in the air or on the ground, but only floored structures are "closed" for insoil-organisms. For example, EFSA (2013a, p. 26 footnote 12) stated, that exposure of bees is negligible when used in glasshouses without honey bees as pollinators.

4.2.2 Equipment and procedures to reduce the escape of an active substance

Other examples of "closed systems" relate to a certain phase in the life of a product. For instance, a bulk transfer system may be perceived as "closed" during mixing and loading but not during application; a bait-box may be perceived as "closed" during most of the use phase but release into the environment can occur via secondary poisoning of predators or on disposal of the container; high-tech greenhouses, usually perceived to be nearly "closed systems", may still result in exposure of operators during mixing and loading or workers on re-entry and leakages into the environment are also possible (EC, 2015).

"Closed mixing/transfer/loading systems" are engineering controls used to protect workers and the environment from dermal hazard when mixing and loading pesticides. Examples of closed systems include: (1) closed mixing/loading systems; (2) closed application systems designed to incorporate pesticides into soil, but only if the system does not allow any pesticide contact with the air throughout the entire application process; (3) water soluble bags while the bag is intact (EPA, 2015).

4.3 Implementation of negligible exposure claims

Identification of an endocrine disruptive substance comprises a comprehensive environmental risk assessment of the substance itself and all metabolites corresponding to the principles as laid down in ECHA (European Chemicals Agency) & EFSA guidance (ECHA and EFSA, 2018).

A substance shall be considered as having ED properties if it meets all of the following criteria (EC, 2018b):

a) it shows an adverse effect in non-target organisms, which is a change in the morphology, physiology, growth, development, reproduction or life span of an organism, system or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress or an increase in susceptibility to other influences;

b) it has an endocrine MoA, i.e., it alters the function(s) of the endocrine system;

c) the adverse effect is a consequence of the endocrine MoA.

To assess these criteria, all ED-relevant information and supporting toxicity information on the substance are collected and assessed. Whether the ED criteria are met will be determined separately with respect to humans and non-target organisms.

A claim of negligible exposure exemption typically follows the identification of an endocrine disruptor. Consequently, the results of endocrine activity and effect from this identification serve as the foundation for an exposure assessment, and the adequacy of existing data determines the applicability of quantitative threshold definitions.

Concerning the environment and non-target organisms, the ED criteria are assessed for various non-target organisms like mammals, fish and amphibians or other taxa (e.g. birds and reptiles). Tests (test guidelines) and parameters that are considered relevant when investigating the ED properties of substances are listed in the OECD guideline 150 (OECD, 2018). These parameters drive the assessment strategy because, by providing evidence for both endocrine activity and the resulting potentially adverse effects, they are considered indicative of an endocrine MoA (ECHA and EFSA, 2018). The assessment strategy comprises five steps: (1) gather all relevant information, (2) assess the evidence, (3) initial analysis of the evidence by means of a decision tree, (4) MoA analysis, (5) conclusion on the ED criteria.

In case a substance has ED properties, the exposure of non-target organisms to that active substance in a PPP - under realistic proposed conditions of use - might be negligible, either because environmental concentrations/exposure/effects are below thresholds (risk-based approach) or because application/authorisation is restricted to uses in closed systems (here closed buildings and permanent greenhouses, hazard-based approach).

To demonstrate negligible exposure below thresholds, exposure assessments are performed (according to existing guidance and models like FOCUS, PERL, PELMO etc.). Environmental fate and behaviour will be evaluated for the representative uses (also considering mitigation measures which might be implemented mandatorily in agricultural practice). Effects of water treatment processes and of transformation products need to be considered. The estimated exposure values are compared with toxicological reference values (thresholds, RAC), being either existing fixed cut-off values (e.g., PEC values) or safe levels as determined through the risk assessment (e.g., normal variation of population size), eventually multiplied by a safety factor (e.g., 1/100).

Negligible exposure below a threshold is applicable only for endocrine active substances affecting non-target organisms when the MoA is known, test systems and RAC are available, and low-dose effects with non-monotonic dose-response relationships are excluded. A conclusion of negligible exposure to the entire environment is reached by demonstrating negligible exposure across all MoA and for all non-target organisms.

If an overall conclusion on negligible exposure of a substance to the environment under practical conditions cannot be demonstrated – either due to exceeded thresholds or because MoA are unknown or test systems are unavailable – restricted uses might be considered. Applying the substance in closed systems such as greenhouses minimises (and thereby probably reduces exposure below threshold) or at best avoids its exposure to the environment. The authorisation of

substances might be restricted to applications in closed systems. Permanent and static structures provided with a translucent outer shell or sealed floor allow to prevent release of plant protection products into certain environmentl compartments with gradually different isolation potential, where stationary, floored structures (greenhouses, closed buildings) have the safest isolation properties according to EFSA (2014a).

5 Conclusions and recommendations

This report aims to present an overview on the use and understanding of the terms „negligible", "no exposure", "negligible exposure", and "negligible concentration" in scientific literature, policy, and law. Based on this, manageable criteria and feasible measures are worked out to define "negligible exposure of non-target organisms to active substances/endocrine disruptors".

Use and definition of the terms were identified by performing a comprehensive literature review and analysing 204 papers from life sciences. The findings have been grouped into three types: narrative, qualitative and quantitative definitions.

Most publications provide a quantitative value for negligible (environmental) concentration/exposure/effect. Different definitions can be found:

- limit of detection (negligible if below the limit of detection)
- effect level (causes a negligible effect)
- threshold (negligible if below threshold value)
- equivalence (negligible if within normal biological variability/ if statistically equivalent)
- significance (negligible if not statistically significant)
- benchmark (negligible if less than reference value)
- probability (negligible if probability is small).

The values in question are derived from scientific studies and expertise in the subject area, ranging between zero and a permissible concentration as determined through appropriate risk assessment.

Also, qualitative and paraphrasing definitions are given, expressing a negligible concentration/exposure/effect in descriptive terms (no, small, unimportant, comparable to control etc.) instead of giving a quantification.

Both quantitative and qualitative definitions presuppose the impracticality of zero tolerance and the availability of knowledge on a substance's hazard and exposure. Nevertheless, both narrative and qualitative definitions should be avoided because these terms can be considered vague and not resilient.

Based on the findings of the review, definitions of "negligible exposure of non-target organisms to active substances/ endocrine disruptors" in the frame of Regulation (EC) No 1107/2009 were worked out, based on the comprehensive environmental risk assessment of substances to identify endocrine disruptive substance properties.

- Exposure is understood to be negligible if demonstrated to be below toxicologically relevant thresholds for the representative uses. This approach requires comprehensive knowledge on a substance's hazard and exposure. For endocrine active substances this can only be demonstrated to non-target organisms, where MoAs are known, validated test systems and RAC are available, and low-dose effects with non-monotonic dose-response relationships are excluded.
- Exposure is understood to be negligible if uses are restricted to closed (as far as it is technically possible) systems. This approach requires knowledge on the equipment and isolation potential of such systems. Gradually more or less closed systems have different isolation

potential, only stationary, floored structures (greenhouses, closed buildings) have the safest isolation properties. This approach is even applicable, if negligible exposure cannot be demonstrated quantitatively to be below toxicologically relevant thresholds for the representative uses.

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A Descriptions of the terms in the literature

This appendix contains the tables with the included titles sorted according to searches 1-4 (A-D).

This is followed by tables (E1-E3) of the 49 included titles of the substance-environment sub-group and the descriptions of methods.

During the extraction process, various elements were collected from the selected publications. These elements comprised among other things *subject area*, *context*, *type* and *definition*. These can be found in the tables for each title. For a clearer understanding, the terms of the table entries are briefly explained here:

Description: This includes the description of the word "negligible" in its entire context - mostly as a citation - from the publication.

Source: This includes the short reference to the source from the publication.

Subject area: All publications were assigned to a subject area, including environment, human health, chemistry, and social sciences etc.

Context: The context describes the connection in which the word "negligible" was used.

Type: The interpretations have been grouped into three types:

- **Narrative definitions** describe or paraphrase the meaning of a term (e.g., using synonyms). This type of definition is typically found in dictionaries and in fact all narrative definitions in this project have been extracted from dictionaries.
  Example: The effect on the heart is negligible if it is of very little importance and not worth considering.

  An overview of all identified narrative descriptions can be found in the main document.

- **Qualitative definitions** list specific criteria that must be met to classify something as negligible or qualitatively state „no" or „very low" or „not observed" or similar.
  Example: The effect on the heart is negligible if the heart rate is not affected.

- **Quantitative definitions** define the term using a numerical value or a range, such as a threshold to be undercut, a value to be met, a probability to be undercut or a range to fall within.
  Example: The effect on the heart is negligible if the heart rate does not change by more than 10%.

Definition: describes the definitions and interpretations of the terms "negligible" "no exposure" or "neglibible exposure" in its application, e.g. as benchmark, threshold, criteria.

A.1 Search 1 "negligible"

A.1.1 Description of the term "negligible" in regulatory context

Description	Source	Subject area	Context	Type	Definition
PEC[4] values for each environmental compartment are compared to thresholds and environmental exposure is considered to be not negligible, if the PEC exceeds the threshold.	ECHA (2016)	environment	exposure	quantitative	threshold
Effect is negligible: 3.5 to 7% for the magnitudes of detrimental impacts on colony, or 'effect sizes' (reduction in colony size) of bees […] guttation occurs for < 10% of location/calendar year combinations. If it is less than 10%, then the exposure is considered as negligible.	EFSA (2013a)	environment	effect	quantitative	threshold
Note that the $PEC_{sw;max}$[5] in the R1 Pond scenario (0.338 µg/L) is lower than the Tier 1 $RAC_{sw;ch}$[6] (0.75 µg/L; see below in chronic risk effect assessment), so that potential risks to aquatic organisms of exposure to fungicide FA are likely negligible.	EFSA (2013b)	environment	exposure	quantitative	threshold
…the exposure of humans to flumioxazin can be considered negligible under the proposed condition of use measured by reference values (ADI[7], ARfD[8], AOEL[9], AAOEL[10], MoE[11])	EFSA (2018b)	human health	exposure	quantitative	threshold

[4] Predicted Environmental Concentration

[5] maximal PEC in surface water

[6] chronic Regulatory Acceptable Concentrations in surface water

[7] Acceptable Daily Intake

[8] Acute Reference Dose

[9] Acceptable Operator Exposure Level

[10] Acute Acceptable Operator Exposure Level

[11] Margin of Exposure

Description	Source	Subject area	Context	Type	Definition
… the exposure of humans to bromoxynil can be considered negligible under the proposed condition of use measured by reference values (ADI, ARfD, AOEL, AAOEL, MoE)	EFSA (2018a)	human health	exposure	quantitative	threshold
criteria for a MS[12] to be recognised as having a 'negligible risk of classical scrapie: the level of confidence that an animal population is 'free' from disease is proportional to (FAO, 2014): - the sample size, i.e. the number of animals sampled; the larger the number of animals submitted to testing, the larger is the likelihood of detecting the disease. - the design prevalence (DP), i.e. the assumed prevalence of disease if it is present and also the probability of infection for each animal in the population; the lower the DP is, the larger will be the effort needed to detect the disease. In ToR[13] 1 it is 0.1%. - the accuracy of the diagnostic test in terms of sensitivity and specificity. Sensitivity is a key factor in terms of both sensitivity of the screening test and sensitivity of the surveillance system, i.e. the probability that the surveillance system would detect disease if it were present.	EFSA (2015c); EFSA (2015b); EFSA (2015a)	animal health	risk	quantitative	criteria
[…] for workers, potential dermal exposure by hand to mouth transfer is generally assumed to be negligible in comparison with that via skin and inhalation.	EFSA (2014b)	human health	exposure	quantitative	benchmark
Environmental exposure is considered to be not negligible, if the PEC exceeds the threshold.	EFSA (2014a)	environment	exposure	quantitative	threshold
A negligible impact is an impact on colony size that is no greater than the normal variability in an "average" colony without pesticide use (median 23.2%).	EFSA (2020)	environment	effect	quantitative	benchmark
Non-dietary negligible exposure can be assumed where levels to which humans are exposed are equal to or lower than natural background levels in the environment, i.e. excluding background levels which have been increased during time by anthropogenic activities and/or which are considered to be a concern.	EC (2015)	human health	exposure	quantitative	threshold

[12] Member State

[13] Terms of Reference

Description	Source	Subject area	Context	Type	Definition
[…] according to the available draft Technical Guidance Document on assessment of negligible exposure, the predicted non-dietary exposure was demonstrated to be below 10% of the (A)AOEL[14] for all groups (operators, workers, bystanders and residents); while at the second tier, the margin of exposure with regard to the carcinogenic effect was higher than 1,000 for all groups.	EFSA (2021a)	plant health	exposure	quantitative	threshold
The expression 'negligible risk research' describes research in which there is no foreseeable risk of harm or discomfort; and any foreseeable risk is no more than inconvenience. Where the risk, even if unlikely, is more than inconvenience, the research is not negligible risk.	National Health and Medical Research Council (2018)	human health	risk	qualitative	description
[…] according to the available draft Technical Guidance Document on assessment of negligible exposure, for the representative use, concentrations of residues of benthiavalicarb-isopropyl < 0.01 mg/kg were only demonstrated for potatoes. However, for the representative use, it could not be excluded that residues in other food items (rotational crops) could occur and be above the level of 0.01 mg/kg.	EFSA (2021a)	plant health	exposure	quantitative	threshold
[…] according to the available draft Technical Guidance Document on assessment of negligible exposure, the outstanding residue data from residue field trials for pome fruit, strawberry and tomato do not allow a conclusion whether residues of clofentezine will be below 0.01 mg/kg or the limit of quantification (LOQ) of the analytical method	EFSA (2021b)	plant health	exposure	quantitative	threshold
It is noted that the RMS[15], co-RMS and one MS[16] disagree with the approach of negligible exposure according to the draft Technical Guidance (European Commission, 2015) and support the use of real exposure studies, if available, to demonstrate that exposure values are below the limit of quantitation to fulfil the criteria of negligible exposure.	EFSA (2021b)	plant health	exposure	quantitative	threshold

[14] (Acute) Acceptable Operator Exposure Level

[15] Rapporteur Member State

[16] Member State

Description	Source	Subject area	Context	Type	Definition
For negligible exposure, RMMs[17] are reflected in the table in case they would lead to exposure below or equal to 10% of the (A)AOEL[18]. […] AAOEL was set at 1 mg/kg bw, on the same basis as the ARfD[19].	EFSA (2021c)	plant health	exposure	quantitative	threshold
With regard to negligible exposure assessment according to the draft technical guidance on assessment of negligible exposure, levels of exposure below 10% of the (A)AOEL were identified for operators, workers, residents and bystanders with relevant risk mitigation measures where necessary.	EFSA (2022a)	plant health	exposure	quantitative	threshold
[…] considering the draft technical guidance on assessment of negligible exposure (European Commission, 2015), the following can be concluded: For the representative uses of triflusulfuron-methyl, residue concentrations of, respectively, IN-M7222 and IN-E7710[20] in sugar beet root (with a possible extrapolation to beet root, fodder beet root and chicory root) were determined by data and are less than 0.01 mg/kg for each compound whilst residues above 0.01 mg/kg are found in sugar beet tops and leaves only.	EFSA (2022a)	plant health	exposure	quantitative	threshold
…no increase in the frequency or magnitude of mortality and visual suffering between exposed and unexposed groups [defined as Surrogate protection goals (SPG) for mammals]; negligible or tolerable effect [SPGs for non-target terrestrial organisms]	EFSA (2022c)	environment	effect	quantitative	description
For the assessment of negligible exposure, only the representative use on potatoes has been considered. Following the available draft technical guidance (European Commission, 2015), no predicted or measured value is below 10% of the (A)AOEL.	EFSA (2023b)	environment	exposure	quantitative	threshold
Regarding the environment, it might be considered that exposure was not negligible, as the available PEC[21] in soil, surface water and sediment for all the representative uses assessed are above levels that can be routinely measured.	EFSA (2023a)	environment	exposure	quantitative	threshold

[17] Risk Mitigation Measures

[18] (Acute) Acceptable Operator Exposure Level

[19] Acute Reference Dose

[20] IN-E7710 and IN-M7222 are major plant and groundwater metabolites of triflusulfuron-methyl

[21] Predicted Environmental Concentration

Description	Source	Subject area	Context	Type	Definition
...a negligible effect on birds and mammals typical for agricultural landscapes can be defined as follows: - It should not exceed the response of the assessment endpoint under baseline conditions (= non-exposed field conditions) within a relevant time period. - This requires a risk assessment with an appropriate statistical power and should be protective of vulnerable and susceptible species from both toxicological and ecological perspective.	EFSA (2023d)	environment	effect	quantitative	benchmark
An effect of pesticides smaller than the normal variability within and between unexposed colonies is considered negligible. An effect is assumed to be negligible if the difference in the sublethal effects between treatment and control is ≤ 10%.	EFSA (2023c)	environment	effect	quantitative	threshold
EPA has used the reactivity of ethane as the threshold of negligible reactivity.	EPA (1977); EPA (2005)	environment	amount	quantitative	benchmark
A 'negligible' assessment means that there are literally no features on the tree that could support a roosting bat, even as a night roost. The majority of these trees are pole stage Western hemlock or Douglas fir and these coniferous species are generally of little value for roosting bats (with the occasional exception of very old trees or dead or dying trees). As such, no further mitigation is required for those trees assessed as being of negligible potential to support roosting bats.	Johns Associates environmental consultants (2010)	environment	potential	qualitative	description

A.1.2 Description of the term "negligible" in scientific literature

Description	Source	Subject area	Context	Type	Definition
In mice treated with repeated doses of T-CAR gel (100 µM), the drug was undetectable in plasma, the heart rate was unaffected, but skin deposition was significantly higher than mice treated with oral carvedilol (32 mg/kg/day). These data indicate that the carbopol-based T-CAR gel holds great promise for skin cancer prevention with negligible systemic effects.	Abdullah Shamim et al. (2022)	human health	effect	qualitative	criteria

Description	Source	Subject area	Context	Type	Definition
A standardized difference of < 0.10 likely denotes negligible imbalance between groups	Al Hilli et al. (2016)	human health	effect	quantitative	statistical threshold
According to the Regulation 2015/1375, derogation from testing is granted in the following situations for swine raised in a negligible-risk compartment: • No autochthonous *Trichinella* infections in domestic pigs (kept in holdings officially recognised as applying controlled-housing conditions) have been detected in the Member State in the past 3 years, during which time, continual testing has been conducted or • Historical data on continual testing carried out on the slaughtered swine population provide at least 95% confidence that the prevalence of *Trichinella* does not exceed 1/1,000,000 in that population or • The holdings applying controlled-housing conditions are located in Belgium or Denmark	Alban and Petersen (2016)	animal health	risk	quantitative	criteria
However, in *Arabidopsis* the activity of MIR159c is so weak it has negligible impact on its potential target genes. Loss of this gene has no noticeable molecular or phenotypic consequence	Allen et al. (2010)	plant health	effect	qualitative	description
There is virtually no chance to bind to free receptors, therefore the health risks are nil or at least negligible.	Autrup et al. (2020)	human health	exposure	qualitative	description
For Eastern location the transpiration was estimated to be between ~0 and 51 mm, […] and negligible at Western location (since cover crop biomass was statistically not different than zero for that site).	Barker et al. (2018)	environment	impact	quantitative	statistical threshold
Levels of microplastics from 100 to 5000 µm span from < 0.0001 to 1.89 mg/L, whereas the most conservative safe concentration is 13.8 mg/L, and probability of exposure is p = 0.00004. Therefore, large microplastics pose negligible global risk.	Beiras and Schönemann (2020)	environment	risk	quantitative	probability
Results seem insignificant owing to minor differences between interventions.	Benjamim et al. (2023)	human health	effect	qualitative	description
Effects of down-regulation on hostplant suitability were minimal, and therefore, pest response was also negligible	Buhl, Strauss, and Lindroth (2015)	plant heath	effect	qualitative	description
The absence of zoonotic *S. suihominis* from any animal in the sample.	Calero-Bernal et al. (2014)	animal health	rate	quantitative	probability

Description	Source	Subject area	Context	Type	Definition
Clinical and economic outcomes were evaluated across 4 ranges of scores (negligible risk, 0 points; low risk, 1 to 2; intermediate risk, 3 to 6; high risk, 7 to 10). […] patients with more than 2 points have only a 24% probability of developing a fistula; but those with 2 or fewer points have a scant (4%) possibility of developing a CR-POPF[22].	Callery, Pratt, Kent, Chaikof, and Vollmer (2013)	human health	risk	qualitative	scores
Likelihood is negligible if the chance of occurrence is so small that can be ignored.	Castiglione et al. (2021)	animal health	risk	quantitative	probability
0.3%–12.5% of global anthropogenic methane emissions are non-negligible.	Cheng et al. (2022)	environment	amount	quantitative	effect level
"Ca. *Brocadia sinica*" became predominant in all the PVA[23] gel-based continuous bioreactors, regardless of seeding source (negligible).	Cho, Choi, Lee, and Bae (2018)	environment	effect	qualitative	description
Clinical progression rate to severe disease, which requires oxygen therapy, was meager [negligible] (1.0/1,290 patient-days; 95% confidence interval, 0 to 13.3/1,000).	Choe et al. (2020)	human health	rate	quantitative	statistical threshold
The MPC[24] is a scientifically derived hazard limit. The NC[25] is simply defined as 1% of the MPC.	Crommentuijn et al. (2000)	environment	concentration	quantitative	threshold
Since methyl bromide fumigations were stopped, no larval interceptions have occurred, reinforcing the fact that the quarantine risk is negligible.	Elvira Villagrán, Willink, Teresa Vera, and Follett (2012)	plant health	risk	qualitative	description
Removals were not statistically different, $p > 0.05$	Fabre et al. (2020)	environment	effect	quantitative	statistical threshold
The maximum average $CVRC^{26}_{Diff}$ was small; 11.3 pp.	Fahlström, Lewén, Enblad, Larsson, and Wikström (2020)	human health	effect	quantitative	value

[22] Clinically relevant postoperative pancreatic fistulas

[23] Poly(vinyl alcohol)

[24] Maximum Permissible Concentration

[25] Negligible Concentration

[26] cerebrovascular reserve capacity

Description	Source	Subject area	Context	Type	Definition
[…] absence of zoonotic parasites in the fish examined. Data are comparable to those reported for the farmed Atlantic salmon, gilthead seabream, European seabass, turbot and marine rainbow trout in previous studies, leading to consider as negligible the risk of anisakid infection in the most important fish species of European mariculture mentioned above.	Fioravanti et al. (2021)	animal health	risk	quantitative	benchmark
The direct effect is a cooling of 0.01 ± 0.005 °C by 2030.	Forster et al. (2020)	environment	effect	quantitative	value
Similarly, the cormorant index significantly contributed to explaining community structure at near-colony points, but its contribution was ecologically negligible (<1%).	Gagnon et al. (2020)	environment	effect	quantitative	statistical threshold
Toxicity treatments achieved negligible toxicity against *D. indicus* and *G. affinis*, with LC_{50}[27] values ranging from 813.16 to 10,459.13 µg/mL.	Govindarajan et al. (2016)	environment	effect	quantitative	value
No effect was observed.	Greenslade et al. (2010)	environment	effect	qualitative	description
Negligible carbohydrate snacks of salads and vegetables contained up to 5.1 g carbohydrate and 276.3 kJ per portion.	Haase, Kahle, Janert, Meier, and Nauck (2017)	human health	amount	quantitative	value
0.5–10 × 10^6 g particulate low-temperature Pyrogenic Carbon per year is exported by the Amazon river.	Häggi et al. (2021)	environment	amount	quantitative	effect level
Stream nutrient concentrations and mass export, and that stream biotic condition is similarly unaffected.	Hensley et al. (2020)	environment	effect	qualitative	description
[…] the extremely low value of S_{PL}[28] (lower than 4.75×10^{-5}) we can safely conclude that ingestion of plastic mass is negligible compared to the mass of ingested prey per unit of time.	Herzke et al. (2016)	environment	effect	quantitative	value
contribution of meteorological factors was negligible (<1%)	Huang and Sun (2020)	environment	effect	quantitative	value
Treatment did not affect the colour and pulling strength of lettuce and cherry.	Ikeura, Kobayashi, and Tamaki (2013)	food	effect	qualitative	description

[27] median lethal dose

[28] fraction of plastic in the ingested food

Description	Source	Subject area	Context	Type	Definition
The risk of HCC[29] was negligible. The cumulative probability of HCC at 1-, 3-, and 5-years among the IT-group was zero, compared to AVT[30]-treated patients with FIB-4 indices <1.45 during the same period: 0.2%, 0.6%, and 1.4%, respectively (P=0.264 for ITT and P=0.533 for per-protocol).	Jeon et al. (2021)	human health	risk	quantitative	statistical threshold
A potential ecological risk is deemed negligible if the „Risk Quotient of Negligible Concentrations" (RQ_{NCs}) is less than 1.	Kalf et al. (1997)	environment	risk	quantitative	threshold
The overall rate of *Enterobius vermicularis* egg positivity was 0.85%.	D.-H. Kim et al. (2015)	human health	effect	quantitative	effect level
Gastrointestinal content and faeces of pyridoxine were less than 0.551% of the oral dose.	D. Y. Lee, Kang, Kim, and Lee (2010)	pharmacology	effect	quantitative	effect level
Dezhou city reached ~ 300 estimated vomiting and diarrhoea patients that may be caused by DON[31] exposure per 100,000 residents. The number is non-negligible even it is less than 5 in 1000.	F. Li et al. (2022)	food	risk	quantitative	threshold
Negligible changes in household carbon footprints compared with 2015 – 2019 levels. The total carbon footprint did not change throughout the period of January – May 2020 compared with the 5 previous years (2015 – 2019).	Long et al. (2021)	environment	effect	quantitative	benchmark
Analyses of all six kinds of rape oil and three kinds of margarines gave results under the limit of detection of 0.02 ng g^{-1} Thallium.	Loula, Kaňa, Vosmanská, Koplík, and Mestek (2016)	food	amount	quantitative	limit of detection
There were no biochar products that had any statistically significant effect across all soils.	Meschewski et al. (2019)	environment	effect	quantitative	statistical threshold
[...] zero cases of recurrence in the MIAB[32] group and two cases (2.9%) in the EUS-FNAB[33] group. This suggests that the impact of MIAB on the postoperative prognosis is negligible.	Minoda et al. (2023)	human health	risk	quantitative	statistical threshold

[29] hepatocellular carcinoma

[30] antiviral therapy

[31] deoxynivalenol

[32] Mucosal incision-assisted biopsy

[33] endoscopic ultrasound-guided fine-needle aspiration/biopsy

Description	Source	Subject area	Context	Type	Definition
Infants' exposure would amount to less than 5% of the usual infant weight-corrected nifurtimox dose (i.e. 10–15 mg/kg/day).	Moroni et al. (2019)	human health	exposure	quantitative	threshold
No significant change in the pharmacokinetics of sulfasalazine was observed after single or multiple administrations of quercetin in rats.	Oh et al. (2021)	pharmacology	effect	quantitative	statistical threshold
Some evidence showing their non-negligible side effects.	Oryan, Alidadi, Moshiri, and Bigham-Sadegh (2014)	human health	effect	qualitative	description
Blood sampling had few negative effects on within-year reproductive success or survival of adult female.	Orzechowski, Shipley, Pegan, and Winkler (2019)	animal health	effect	qualitative	description
There were no differences in growth between any of the treatment groups and the control group (F321 = 0.49, p = 0.69).	Payne et al. (2019)	environment	effect	quantitative	statistical threshold
[…] a therapeutic change occurred only in about 1% of all surfaces. Hence, a negligible therapeutic impact of the radiographs on the decision made using visual inspection alone was observed.	Pontes et al. (2021)	human health	effect	quantitative	statistical threshold
The likelihood of an event is 0 - 10^{-6}; i.e. it almost certainly not occurs.	Powell (2013)	environment	probability	quantitative	probability
Early development of derived offspring, in terms of hatching rate, body length, malformation rate and mortality rate, did not significantly differ from that of the control.	Qiang et al. (2020)	environment	effect	quantitative	statistical threshold
GE[34] crop plants that can be predicted to pose low or negligible risk under conditions of LLP[35] in seed. Three general criteria are proposed: 1. Experience and knowledge with the crop plant indicates that the crop will not survive, persist and multiply in the receiving environment without human intervention 2. Experience and knowledge with the incorporated trait (either phenotype or gene/protein) indicates that it does not pose a risk to the environment under conditions of LLP in seed	Roberts et al. (2015)	plant health	risk	qualitative	criteria

[34] genetically engineered

[35] low-level presence

Description	Source	Subject area	Context	Type	Definition
3. Environmental risk assessment concludes that the GE crop plant does not have altered characteristics with respect to growth or reproduction that would affect survival and persistence in the receiving environment					
Results indicate levels of contamination below the maximum levels tolerated by international standards in groundnut samples.	Santis et al. (2021)	environment	amount	quantitative	threshold
Serum 25OHD2 levels accounted for less than 5% of serum 25OHD level.	Sarathi, Reddy, and Tirupati (2021)	human health	amount	quantitative	effect level
No significant effect of X-ray µ-CT[36] on CO_2[37] production was observed.	Schmidt, Vetterlein, Köhne, and Eickhorst (2015)	environment	effect	quantitative	statistical threshold
No significant differences between the exposure organisms and the corresponding controls were detected.	Scopetani et al. (2020)	environment	effect	quantitative	statistical threshold
Products contained 0.014–1.02 µg/day of triiodothyronine and 0.57–0.90 µg/day of thyroxine.	Seger et al. (2017)	food	amount	quantitative	value
Ani9[38] not affect ANO2[39] activity at the same concentration.	Seo et al. (2016)	pharmacology	effect	qualitative	description
There were no significant differences (P > 0.05) in mean pain scores at each of the four days.	Shah et al. (2013)	human health	effect	quantitative	statistical threshold
Ursodeoxycholic acid concentrations in breast milk were 0.69 µmol/L.	Šimják et al. (2022)	human health	concentration	quantitative	value
The hot dogs cooked on freshly cut oleander skewers contained a mean of 7.0 ppb of oleandrin with a SD of 2.1 ppb (range: 5.2–10 ppb).	Suchard and Greb (2021)	food	amount	quantitative	value

[36] X-ray Microfocused Computed Tomography

[37] carbon dioxide

[38] inhibitor 2-(4-chloro-2-methylphenoxy)-N-[(2-methoxyphenyl)methylideneamino]-acetamide

[39] transmembrane protein

Description	Source	Subject area	Context	Type	Definition
None exceeded the TWI[40], and risk of kidney damage from mercury exposure is therefore negligible.	Suomi, Valsta, and Tuominen (2021)	human health	effect	quantitative	threshold
Increases of DIN[41] and $Si(OH)_4$[42] concentrations could not be observed.	Tada, Koomklang, Ichimi, and Yamaguchi (2017)	environment	effect	qualitative	description
Groups showed the similar values to saline-treated group.	Takemoto et al. (2020)	pharmacology	effect	qualitative	description
[...] no significant statistical difference between groups. That several doses of DLBS3233 (from 50 mg up to 400 mg once daily for 3 days) did not affect fasting blood glucose levels of healthy subjects, demonstrated the negligible risk of DLBS3233 in developing hypoglycemia.	Tjandrawinata, Suastika, and Nofiarny (2012)	pharmacology	risk	quantitative	statistical threshold
Only traces of harmful metals were found in honey (<0.015 and <0.043 mg/kg).	Tomczyk, Zaguła, Kaczmarski, Puchalski, and Dżugan (2023)	food	amount	quantitative	effect level
[…] immunogenicity was negligible (Incidence <3%) in the presence of IFX[43] concentrations greater than 5 µg/mL, irrespective of 6-TGN[44] levels.	Ungaro, Colombel, Dubinsky, Jain, and Dervieux (2022)	pharmacology	effect	quantitative	statistical threshold
No interference peaks or matrix effects were observed.	Vats, Verma, and Monif (2017)	pharmacology	effect	qualitative	description
Damage by potato stalk borers did not have a significant impact on any of the plant performance measures	Wise (2018)	plant health	effect	quantitative	statistical threshold
[…] difference in mean time to LOE[45] of ~2.4 min […] may be negligible because the median time to LOE can vary substantially (up to 114.8 min) between families of Atlantic salmon.	Wood, Clark, Andrewartha, Elliott, and Frappell (2017)	animal health	effect	quantitative	benchmark

[40] tolerable weekly intake

[41] dissolved inorganic nitrogen

[42] Silicic acid

[43] Infliximab, a chimeric monoclonal antibody targeting tumor necrosis factor-α

[44] 6-thioguanine

[45] loss of equilibrium

Description	Source	Subject area	Context	Type	Definition
Acute hypoxia tolerance was lower (2.5% increased dissolved oxygen for fish exposed to 1250 ppm hydrogen peroxide at 12°C).	Wood, Taylor, Quezada-Rodriguez, and Wynne (2021)	animal health	effect	quantitative	value
Regardless of the particle polymer, type and size showed non-significant effects ($p < 0.05$) on the enzyme activities.	Xu et al. (2020)	environment	effect	quantitative	statistical threshold
The 5-year cumulative needle tract seeding rate was 3.8% (95%CI: 1.6%-7.8%, non-neglible).	Yane et al. (2020)	human health	effect	quantitative	statistical threshold
[…] exposure levels that harmed the larvae in the current study are far greater than natural exposure levels. […] consumption of Bt[46] rice pollen will pose a low to negligible risk to *B. mori*.	Yang et al. (2014)	environment	exposure	quantitative	threshold
Infection was negligible by absence of frass ejection from pine bonsai trunks.	Yasuda et al. (2020)	plant health	effect	qualitative	description
[…] the perinatal tulathromycin metaphylaxis has no measurable benefits or detriment impacts on fecal microbiota structure and abundance of antimicrobial resistance genes in pre-weaned piglets.	Zeineldin et al. (2019)	animal health	effect	qualitative	description
[…] half-lives of PCP[47] in biological samples (from 30 h to more than 10 days), long-term accumulation and storage of small amounts) suggests that even for populations being exposed to low environmental levels of PCP in the schistosomiasis epidemic areas in China, their long-term health risk is not negligible.	Zheng, Yu, Wang, and Qu (2012)	human health	effect	qualitative	criteria
Adjusted smoking prevalence showed no detectable decline (from 33.8% in 1997 to 31.8% in 2013, trend test P= 0.13).	Zhu, Anderson, Zhuang, Gamst, and Kohatsu (2017)	human health	effect	quantitative	statistical threshold
The 99th percentile of the electric field is very stable, is almost unchanged.	Zilberti, Bottauscio, and Chiampi (2015)	human health	effect	quantitative	statistical threshold

[46] *Bacillus thuringiensis*

[47] Pentachlorophenol

A.2 Search 2 "no exposure"

A.2.1 Description of the term "no exposure" in regulatory context

Description	Source	Subject area	Context	Type	Definition
"No Exposure" shall mean that all industrial materials and activities are protected by a storm-resistant shelter to prevent exposure to rain, snow, snowmelt, run-on and/or runoff. Industrial materials or activities include, but are not limited to, material handling equipment or activities, industrial machinery, raw materials, intermediate products, byproducts, final products not intended to be used outdoors, or waste products. Material handling activities include the storage, loading and unloading, transportation, or conveyance of any raw material, intermediate product, final product or waste product.	Ordinances Governing (2022)	environment	exposure	qualitative	descrip-tion

A.2.2 Description of the term "no exposure" in in scientific literature

Description	Source	Subject area	Context	Type	Definition
No heat-exposure risk group spend <25% of their work hours at high temperatures.	D. Kim and Lim (2017)	human health	exposure	quantitative	description
According to European Radiation Safety Standards […] radiation exposure should not exceed 1mSv/y for the body, 25mSy/y for the thyroid, and 50mSv/y for the hand.	J.-E. Lee et al. (2019)	human health	exposure	quantitative	threshold
A negligible duration of sun exposure: < 10 minutes a day	Rezaiian et al. (2022)	human health	exposure	quantitative	threshold
For NO_2[48], nearly all samples showed concentrations of 0 ppm.	Cox, Sleeth, Handy, and Alaves (2019)	human health	exposure	quantitative	threshold

[48] Nitrogen Dioxide

Description	Source	Subject area	Context	Type	Definition
Unrecognized exposure may cause most Malignant mesothelioma cases initially regarded as "no exposure."	Musk et al. (2017)	human health	exposure	qualitative	description
Non-exposed populations, i.e., the populations with no anthropogenic exposure to cadmium in a single nation of Japan.	Sakuragi et al. (2012)	human health	exposure	qualitative	description
No previous exposure to Neuromuscular blocking agents who is confirmed by skin tests.	Choi, Yi, and Rha (2013)	human health	exposure	qualitative	description
[…] the plasma concentrations were below the limit of quantification in all samples.	Dimiou et al. (2022)	pharmacology	concentration	quantitative	limit of detection

A.3 Search 3 "negligible exposure"

A.3.1 Description of the term "negligible exposure" in regulatory context

Description	Source	Subject area	Context	Type	Definition
Negligible exposure to humans [is given if] residue situation for isoxaflutole and metabolite RPA 202248 in conventional maize commodities at harvest in the available field trials is consistently below the individual limit of quantifications (LOQs) of 0.01 mg/kg (sum LOQ 0.02 mg/kg) of the validated analytical method."	EFSA (2017a)	human health	exposure	quantitative	threshold
"The exposure of groundwater to this metabolite is not expected to meet the approval criteria provided for in Article 4 of Regulation (EC) No 1107/2009, and consequently, it cannot be considered negligible from the point of view of the draft technical guidance (European Commission, 2015), (when) the parametric drinking water limit of 0.1 µg/L has been identified as a critical area of concern (EFSA, 2014b) for the relevant metabolite CGA371075 in all the pertinent groundwater scenarios for all four representative uses assessed."	EFSA (2017b)	human health	exposure	quantitative	threshold

Description	Source	Subject area	Context	Type	Definition
"For the representative uses of ipconazole, residue concentrations of the active substance ipconazole in grain and straw of wheat and barley, in potential succeeding crops and in food items of animal origin were determined by data or can be reasonably expected to be less than 0.01 mg/kg. In a consumer dietary risk assessment for parent ipconazole using PRIMo rev.3.1 (Appendix B), chronic dietary exposure was less than 1% of the ADI[49] for ipconazole and the maximum acute dietary exposure was 1% of the ARfD[50] (wheat, UK, 4–6 years) for ipconazole. Consumer exposure to ipconazole via drinking water is also unlikely for the representative uses, based on the peer-reviewed groundwater exposure assessments (EFSA, 2013a)."	EFSA (2022b)	human health	exposure	quantitative	threshold

A.3.2 "Negligible exposure" concentrations or concentrations causing "negligible" effects described in scientific literature

Description	Source	Subject area	Context	Type	Definition
"…negligible exposure must fall somewhere between ''no exposure'' (i.e. nominal concentrations of 0, or less than the limit of detection/limit of quantification) and a concentration representing an acceptable or low risk."	Bars et al. (2012)	human health	exposure	qualitative	description
A non-negligible exposure to citrinin is given if exposure of children was 0.05 µg/kg bw per day (i.e., 25% of the pTDI[51]).	Degen et al. (2023)	human health	exposure	quantitative	threshold
A total of 10.4 million workers in the UK are employed in jobs (representing 22.6% of jobs held) identified as likely to experience some degree of exposure to SHS[52] at work. Our threshold of '10% of the workers within that code being exposed' thus equates to at least 1.04 million workers exposed to SHS at work. (non-negligible exposure)	Dobson, Demou, and Semple (2021)	human health	exposure	quantitative	threshold

[49] Acceptable Daily Intake

[50] Acute Reference Dose

[51] provisional tolerable daily intake

[52] Second-Hand Tobacco Smoke

Description	Source	Subject area	Context	Type	Definition
All HQs and HIs[53] of the pesticides were < 1 for all population groups (adults, children, and infants), indicating negligible exposure risks.	Duong, Doan, Trinh, and Kadokami (2021)	human health	exposure	quantitative	threshold
"the exposure…is negligible" when "the [plant protection] is used in closed systems".	Friessleben and Graef (2016)	human health	exposure	qualitative	description
VNT1 protein levels were below the detection limit. Both humans and livestock have negligible exposure to VNT1 from late blight protected potatoes, even using conservative assumptions. It can be concluded that human and livestock exposure to VNT1 from late blight protected potatoes is negligible.	Habig, Rowland, Pence, and Zhong (2018)	food	exposure	quantitative	limit of detection
>0.1 µg/m^3 define the presence of "exposure" to airborne beryllium.	Hamm and Burstyn (2011)	human health	exposure	quantitative	limit of detection
A negligible exposure dosage from breastfeeding of tenofovir is estimated at 0.4 – 2.1 mg/ kg/day, which represented 0.01 – 0.04% of the proposed pediatric therapeutic daily dose of 6 mg/kg/day.	Hu, Wang, and Xu (2019)	human health	exposure	quantitative	threshold
The NEDI[54] for U.S. consumer exposure to EBDCs [55]and ETU[56] was 0.000027 mg/kg bw/day, calculated as ETU, or less than 1% (0.68%) of the 0.004 mg/kg bw/day ADI[57] for ETU.	Hurt et al. (2010)	human health	exposure	quantitative	threshold
Exposure to organochlorines remain insignificant. Exposure did not show any association with the severity of otitis media in the proportional odds model.	Jensen, Koch, Homøe, and Bjerregaard (2013)	human health	exposure	quantitative	threshold statistical
A non-negligible Mercury exposure for a 1 kg infant were 0.09 mg/kg/d which approximates the daily reference dose recommended by the Environmental Protection Agency (0.1 mg/kg/d).	Jering et al. (2015)	human health	exposure	quantitative	threshold
Glyfonova induced only minor effects on steroidogenic gene expression. Two Leydig cell-specific steroidogenic genes Cyp11a1 and Cyp17a1 were	Johansson et al. (2018)	animal health	exposure	qualitative	description

[53] Hazard Quotients (HQs); Hazard Index (HI)

[54] National Estimate of Daily Intake

[55] Dialkyldithiocarbamates

[56] Common metabolite of EBDCs: ethylenethiourea

[57] Acceptable Daily Intake

Description	Source	Subject area	Context	Type	Definition
upregulated in the NOVA (Glyfonova® 450 Plus) exposed group. Although testosterone levels were unchanged in the same animals, this indicates some degree of disruption to testis function that could potentially be exasperated at higher doses.					
Despite being orders of magnitude higher than others, the highest PrHE[58] estimated in this study, which, for a 3-year-old exposed to acrolein, was still negligible (<1 in a million).	D. Li and Li (2021)	human health	exposure	quantitative	value
Negligible exposure from the application of the plant spray (pump spray) was observed. Spraying of product IV resulted in by scanning mobility particle sizer signals similar to the background signal irrespective of the dispensed spray amount.	Lorenz et al. (2011)	human health	exposure	quantitative	limit of detection
Non-negligible exposure levels to Citrinin ranged from 8% to 40% of the provisional tolerable daily intake of 0.2 µg/kg bw per day, which corresponds to the level of no concern for nephrotoxicity	Narváez, Izzo, Rodríguez-Carrasco, and Ritieni (2021)	food	exposure	quantitative	threshold
TCS and TCC[59] exposure from consumption of plant tissue grown in biosolids-amended soil is negligible relative to the ADI[60] value (0.08 mg/kg body weight per day)	Prosser, Lissemore, Topp, and Sibley (2014)	human health	exposure	quantitative	threshold
Exposure of users of ECs, HTPs, and NRTs to TSNAs[61] as well as the minor tobacco alkaloids AB and AT[62] is marginal and statistically not distinguishable from that of Non-users (p<0,05)	Scherer, Scherer, Mütze, Hauke, and Pluym (2022)	human health	exposure	quantitative	threshold statistical
Environmental tobacco smoke exposure was classified as negligible (cotinine concentrations below sex and race/ ethnicity cut–points for smokers)	Sutton, Ranney, Wilder, and Sanders (2012)	human health	exposure	quantitative	threshold

[58] Combined ingestion and inhalation exposure as a fraction of ED_{50} and estimated probability of occurrence of health effects

[59] triclosan (TCS) and triclocarban (TCC)

[60] Acceptable Daily Intake

[61] electronic cigarettes (ECs), heated tobacco products (HTPs), nicotine replacement therapy products (NRTs), and Tobacco-specific nitrosamines (TSNAs).

[62] alkaloids anabasine (AB) and anatabine (AT)

Description	Source	Subject area	Context	Type	Definition
These early-life differences in gut bacterial community structures marginally persisted into adulthood (Adonis R2 = 9.87%, P = .061). Overall, these findings confirm a minor role for environment on gut microbial composition during early life.	Tasnim et al. (2021)	human health	effect	quantitative	threshold statistical
Defining a fixed number, comparable to the groundwater cutoff value of 0.1µg/L, below which concentrations are considered negligible, is not deemed a science-based approach and thus not advocated here. As negligibility is not defined in the regulations, it is implied to lie somewhere between zero and a regulatory acceptable concentration as determined through an appropriate risk assessment. Obviously, negligible exposure can only be defined for chemicals where there is agreement on a toxicological threshold for endocrine-mediated adverse effects.	Weltje et al. (2013)	environment	exposure	qualitative	description

A.4 Search 4 "Negligible concentration"

A.4.1 "Negligible concentration" described in scientific literature

Description	Source	Subject area	Context	Type	Definition
The sample contains negligible concentrations of other chromophores (<10ppma[63] V^{3+}; Cr^{3+}; Co^{2+})[64].	Belley and Palke (2021)	earth science	concentration	quantitative	limit of detection
Mercury concentrations varied greatly between macrophyte species, with relatively high concentrations in *Utricularia vulgaris* (>80 ng g^{-1} in some sites), and negligible concentrations in *Nuphar variegata* (~6 ng g^{-1}).	Bergman and Bump (2014)	environment	concentration	quantitative	value
The very low amounts of chlorinated metabolites	Braeckevelt et al. (2011)	environment	concentration	quantitative	description

[63] Parts Per Million Atoms; 1ppma is a fraction of 1 in 10^6 atoms

[64] Vanadium cation V^{3+}; chromium cation Cr^{3+}; cobalt cation Co^{2+}

Description	Source	Subject area	Context	Type	Definition
The [negligible] concentrations of heavy metals were below the maximum allowable limit for use in agriculture according to the Romanian legislation OM 344/2004 (Cu 500 mg/kg, Zn 2000 mg/kg, Pb 300 mg/kg, and Cd 10 mg/kg)[65].	Burducea et al. (2022)	environment	concentration	quantitative	threshold
Chaoborus transported methane (CH_4) from the hypolimnion to the lower epilimnion at dusk, but the overall rate of CH_4 transport was minor (~0.1 mmol CH_4 m^{-2} yr^{-1}; <1% of total CH_4 diffusive flux during the summer stratified period).	Carey et al. (2018)	environment	concentration	quantitative	value
The CP/HM[66] cement elutes a negligible concentration of the drug; (minimum therapeutic concentration of vancomycin is approximately 1.5 µg mL^{-1})	Chung et al. (2014)	pharmacology	concentration	quantitative	threshold
[…] *S. aethiopicus* extract had non-negligible concentrations [16.23 ± 0.54 yield in %] of polyphenols, flavonoids, and tannins, which could confer it an antioxidant effect.	Dadaya, Koubala, Abaissou, Zingue, and Ndjonka (2021)	human health	concentration	quantitative	value
Negligible Concentrations (NC; concentrations above which possible effects of combination toxicity due to the presence of other substances are considered). NC value was calculated as MPC/100; MPC: Maximum Permissible Concentrations: concentrations above which the risk of adverse effects is considered unacceptable).	Dauner et al. (2018)	environment	concentration	quantitative	threshold
Negligible concentrations of ammonium were detected (average below detection limit of 1.0 µg ml^{-1}).	Davenport et al. (2012)	environment	concentration	quantitative	limit of detection
Non-negligible concentrations of elemental carbon were also observed (0.36 µg/scm, [7% of PM[67]], confirming that light-absorbing aerosol produced from combustion sources can be efficiently transported up the altitudes of Himalayan glaciers.	Decesari et al. (2010)	environment	concentration	quantitative	value

[65] copper Cu; zinc Zn; lead Pb; cadmium Cd

[66] Calcium phosphate (CP)/ hollow microsphere (HM)

[67] particulate matter

Description	Source	Subject area	Context	Type	Definition
with a negligible concentration [with only a shallow content] of toxic elements such as Manganese, Cobalt, Nickel, Copper, Lead (Pb), Cadmium, Chromium, Arsenic (As), and Silver, indicating a good nutritive value of the extracted oil. concentrations of elements, Pb and As […] were less than the acceptable level (Pb: 0.5 mg/kg, As: 0.1 mg/kg) for food and feed according to FAO[68] and Codex Standards	Ferdousi et al. (2023)	food	concentration	quantitative	threshold
The plants were grown in perlite with recycling nutrient solution, which was prepared with negligible concentration of NaCl[69] [FWLB: fresh water (negligible NaCl concentration) with 0.5 mg L^{-1}].	Guidi et al. (2011)	environment	exposure	quantitative	value
negligible nitrate (<0.002 mM) and sulfate concentrations (<1 mM). These samples belong to various groundwater types and had negligible methane concentrations <0.01 mM. […] nitrate (>0.006 mM) concentrations are not negligible.	Humez et al. (2016)	environment	concentration	quantitative	value
The acid generation potential (AP) was negligible for all samples (<3 kg $CaCO_3$[70]/t).	Kandji et al. (2017)	environment	concentration	quantitative	value
We found […] negligible concentrations [bBDL-0.08 ng/L[71]] in the samples from background zones. Flame retardants in the water samples of the background zones were almost non-detected […].	Khan et al. (2016)	environment	concentration	quantitative	limit of detection
Electron microprobe analysis on natural scorodites confirms that they contain negligible concentrations of antimony (Sb). Two of the samples showed no detectable amounts of Sb (LOD[72] = 0.005 wt.%). Others showed minimal Sb [0.009 wt.% to a maximum of 0. 615 wt.%].	Kossoff, Welch, and Hudson-Edwards (2015)	earth science	concentration	quantitative	limit of detection

[68] Food and Agriculture Organization of the United Nations

[69] sodium chloride

[70] Calcium carbonate

[71] Below Detectable Level

[72] Limit of detection

Description	Source	Subject area	Context	Type	Definition
Low/ negligible content of Iridium and Osmium, which are close to the detection limit.	Kvasnytsya et al. (2013)	earth science	concentration	quantitative	limit of detection
When the heme concentrations were below 1 µM, between 1 µM and 5 µM and above 5 µM, production of anti-BSA IgG and IgM was unaffected.	G. Li, Xue, Fan, and Bai (2017)	animal health	concentration	quantitative	effect level
For most polycyclic aromatic hydrocarbons, the risk quotient of negligible concentrations (RQ_{NCs}) exceeded 1 and the risk quotient of maximum permissible concentrations (RQ_{MPCs}) was less than 1, indicating a middle-level ecological risk.	R. Li et al. (2019)	environment	concentration	quantitative	threshold
Novel PFASs[73] accounted for a considerable percentage of total PFASs in pregnant women and can be transferred to fetuses at non-negligible concentrations (i.e., 27.9% and 30.3% of total PFAS intensities in maternal and cord sera, respectively).	Y. Li et al. (2020)	human health	concentration	quantitative	value
Applying the Toutain model approach an effective plasma concentration (EPC) of caffeine was estimated at 3.05 µg/mL, irrelevant concentrations in blood (IPC) and urine (IUC) approached 6 and 12 ng/mL, respectively. EPC of theobromine was calculated with 3.80 µg/mL, and irrelevant concentrations of theobromine were determined at 8 ng/mL in plasma and at 142 ng/mL in urine. Toutain modelling of the theophylline data produced an EPC, IPC, and IUC of 3.20 µg/mL, 6 ng/mL, and 75 ng/mL, respectively.	Machnik et al. (2017)	pharmacology	concentration	quantitative	threshold
Onion and extra-virgin olive oil (EVOO) were more effective in limiting oxidation than the other foods, resulting in negligible concentrations (undetectable levels) of lipid hydroperoxides after digestion.	Martini, Conte, Bottazzi, and Tagliazucchi (2020)	human health	concentration	quantitative	limit of detection
Presence of a considerable percentage of silicon (Si) and lead (Pb) in erythrocytes of the fish collected from the polluted lake, in contrast to a negligible concentration of the two elements in control fish (Si: 0.72 ± 0.01 and 0.35 ± 0.01; Pb: was not detected)	Massar et al. (2012)	environment	exposure	quantitative	limit of detection

[73] Per- and polyfluoroalkyl substance

Description	Source	Subject area	Context	Type	Definition
content of undesirable BLG[74] was very low and negligible; the BLG content was reduced to nondetectable content (~ 0 ppm in 85°C)	Mirabzadeh et al. (2015)	pharmacology	concentration	quantitative	limit of detection
In meat, the most detected veterinary drugs were antibiotics generally at negligible concentrations (<10 µg kg^{-1}, according to STCs[75])	Moretti et al. (2020)	food	concentration	quantitative	threshold
3SH and 3SHA[76] are present in negligible concentrations in the grape berry, juice (60 ng L^{-1}, 4.2 ng L^{-1}, and 3 ng L^{-1})	Muhl, Pilkington, Fedrizzi, and Deed (2022)	food	concentration	quantitative	value
Serum vancomycin levels were observed to be highest at 6 hours in negligible concentrations of 6.06 ± 2.2 µg/mL.	Naresh-Babu and Arun-Kumar (2020)	pharmacology	concentration	quantitative	value
Because plasma concentrations of LC15-0636 were lower than the lower limit of quantification, the exposure of LC15-0636 was negligible when gemigliptin was administered concurrently with ketoconazole pretreatment.	Noh et al. (2012)	pharmacology	concentration	quantitative	limit of detection
Elements like, K, Ca, Fe, and Mn[77] were found to be in negligible concentrations [< 0.001 wt. %] in all the samples.	Ogbuefi, Nwaokafor, Njoku, and Uzuegbunam (2020)	food	concentration	quantitative	value
[…] Gypsic Haploxerepts defined had negligible concentrations of gypsum in the surface mineral horizon (less than 30 $mg \cdot g^{-1}$) but gypsic horizons deeper in these soils had concentrations of 320–970 $mg \cdot g^{-1}$.	Olarieta et al. (2016)	environment	concentration	quantitative	value
HF[78] was undetectable in serum and kidneys, and detected at negligible concentrations in liver and lungs [mean concentrations ± STD for liver and lungs were 0.0084 ± 0.009 mg/g and 0.0008 ± 0.002 mg/g, resp.]	Peyton et al. (2012)	human health	concentration	quantitative	value

[74] β-lactoglobulin

[75] Screening Target Concentrations; EU

[76] Volatile polyfunctional thiol compounds, 3-sulfanylhexan-1-ol (3SH), 3-sulfanylhexylacetate (3SHA)

[77] Potassium K; Calcium Ca, Iron Fe, and Manganese Mn

[78] Halofuginone is a type-1 collagen synthesis inhibito

Description	Source	Subject area	Context	Type	Definition
Seeds of *O. gratissimum L.* grown in polluted soil contained undetectable to negligible concentrations of cadmium. […]The maximum cadmium content (0.03 µg g^{-1}) was detectable only in the seeds from *O. gratissimum L.* plants treated with EDTA[79]. Cadmium contents in the seeds of other treatments were lower than 0.01 µg g^{-1}.	Prapagdee and Khonsue (2015)	environment	concentration	quantitative	value
Negligible concentrations of tentoxin were determined 24 h after harvest [0.6-9 ng/g]. Considering the sample weights (A) of <0.1% of the respective total apple batch, the contamination is clearly negligible.	Puntscher, Marko, and Warth (2020)	food	concentration	quantitative	value
[…] these reefs were categorically graded according to levels of likely exposure (Negligible, Occasional exposures >5 ppm, Repeated exposures <5 ppm). […] quantities of settling material at these two reefs to have likely been several orders of magnitude less than at the other reefs—negligible quantities of material.	Purser (2015)	environment	exposure	qualitative	description
[…] fluoride (F^-) concentration of all concentration of study samples of bottled as well as bubble top can packaged drinking water was found to be very low and almost negligible, which is much below the stipulated values specified in Indian and International standards.	Ray, Roy, and Majumder (2016)	food	concentration	quantitative	threshold
[…] two dietary treatment groups: (1) 42 mg Zn[80]/kg diet from ingredients only (unsupplemented, marginal dietary Zn concentration below Zn requirements of 80 mg Zn/kg feed); and (2) 106 mg Zn/kg diet, where Zn was added as ZnO (common commercial dietary Zn concentration).	Riet et al. (2016)	animal health	concentration of substances (chemicals)	quantitative	threshold
Cr: 0.154 mg/L to 0.215 mg/L, Cu: 0.035 mg/L to 0.072 mg/L and Cd[81] (<0.004 mg/L) were found in negligible concentrations in the waste-water from the use of natural dye extracts. Although the Cr content met the quality standards of the KEPMENLH[82] and World Bank (<1.000 mg/L), it did	Rosyida et al. (2022)	environment	concentration	quantitative	threshold

[79] Ethylenediaminetetraacetic acid

[80] zinc

[81] chromium Cr; copper Cu; cadmium Cd

[82] "Liquid waste quality standards for industrial activities" Ministry of the Environment, Jakarta, Indonesia. "MEN-LH/KEP-51/10/1995.

Description	Source	Subject area	Context	Type	Definition
not meet the higher standards of the US EPA[83] (<0.100 mg/L) the WHO[84] (<0.050 mg/L).					
The salt concentration used in Belgian minced chicken meat preparations of approximately 1.5% had no impact on the number of *Campylobacter spp.* recovered during storage time.	Sampers, Habib, Zutter, Dumoulin, and Uyttendaele (2010)	food	concentration	quantitative	effect level
Maize […] produced about 10 gm in dry weight but its concentration of Chromium in leaves was negligible (about 0.34 mg/kg).	Shams et al. (2010)	environment	exposure	quantitative	value
Our livestock operations contributed negligible concentrations of phosphorus to groundwater (0.67 mg L^{-1}) and surface water (0.55 mg L^{-1}).	Sigua et al. (2010)	environment	concentration	quantitative	threshold
[…] it was found that the leaching of hazardous heavy metals from EAF[85] slag is negligible or within permissible limits as per IS 383−2016 and EPA.	Singh et al. (2021)	environment	concentration	quantitative	threshold
REEs[86] were found in apples at negligible values, their sum (ΣREE) ranging from 0.0025 to 0.016 mg kg^{-1}, with the main contribution of scandium.	Squadrone et al. (2020)	food	concentration	quantitative	value
Oxytetracycline is a common antibiotic in aquaculture with minor concentrations of 0.8–6.3 µg g^{-1} regularly observed in sediments of fish farms.	Sundberg and Karvonen (2018)	environment	exposure	quantitative	value
The concentration of PCP[87] in the plasma of test animals continued to increase […] while that of animals that received PCP via buccal administration was below the detection limit […], and it was 0.744 ± 0.364 ng/mL at 180 min.	Tanaka et al. (2022)	pharmacology	concentration	quantitative	limit of detection

[83] U.S. Environmental Protection Agency

[84] World Health Organization

[85] electric arc furnace

[86] rare earth elements

[87] Pilocarpine

Description	Source	Subject area	Context	Type	Definition
Al, Mo, and Ni[88] were detected in some samples of wheat and barley of all origins, whereas other elements were at very low levels considered to be negligible concentrations. All of these elements naturally occur in the environment and foods (but no MRL[89] has been estimated in foods).	Thabit, Shokr, Elgeddawy, and El-Naggar (2021)	food	concentration	quantitative	value
GHB-Gluc[90] was found in negligible concentrations with no differences to those of control individuals. GHB-Gluc was found only in traces (under the LOQ and above the LOD[91]) in all the analysed plasma samples, with no difference with zero time indicating that GHB-Gluc blood concentrations are not affected by sodium oxybate administration.	Tittarelli et al. (2017)	pharmacology	concentration	quantitative	limit of detection
Tail tissues of all samples contained negligible Paralytic shellfish toxin levels (<0.02 mg of STX[92] 2HCl eq/kg).	Turnbull, Malhi, Tan, Tim Harwood, and Madigan (2018)	food	concentration	quantitative	value
[…] negligible *in-vitro* release up to 3 h and *In-vivo* organ distribution study of coated PZM[93] show negligible concentration (8.12 ± 0.15 w/v[94]) of drug in stomach and intestine in first 6 h in compared to uncoated (50.82 ± 0.85 w/v) and pure drug (98.68 ± 0.68 w/v).	Vaibhav and Dangi (2012)	pharmacology	concentration	quantitative	value
The potential ecological risks of PAHs[95] and heavy metals (dosage: 1%, w/w; frequency: 1) were minimal according to the risk quotient of negligible concentrations (RQ_{NCs}:2.50–47.40, << 800) and maximum permissible	Zhang et al. (2018)	environment	concentration	quantitative	threshold

[88] aluminium Al; molybdenum Mo, and nickel Ni

[89] Maximum Residue Limit

[90] sodium salt of γ- hydroxybutyric acid and its metabolite GHB-glucuronide in blood

[91] Limit of quantification LOQ and Limit of detection LOD

[92] saxitoxin

[93] Pectin:Zn-acetate microspheres

[94] Weight per volume

[95] polycyclic aromatic hydrocarbons

Description	Source	Subject area	Context	Type	Definition
concentrations (RQ_{MPCs}:0.02–0.48, << 1) for PAHs and the potential ecological risk indexes (PERI: 0.01–0.28, << 150) for heavy metals.					

B Descriptions of methods from the 49 publications comprising the substance-environment subgroup

B.1 Methods in context of "concentration"

Description of methods	Source	Type	Definition
An environmental concentration (chlorinated metabolites in outflow) is measured. Without providing a specific cutoff value, the environmental concentration is assumed to be negligible due to being very small.	Braeckevelt et al. (2011)	quantitative	description
An environmental concentration (heavy metals in soil) is measured. The environmental concentration is assumed to be negligible for multiple reasons: It was small compared to other studies, it was lower than a legal threshold and in one case it was lower than a limit of detection.	Burducea et al. (2022)	quantitative	threshold
A methodology that is used to derive the MPCs[96] and NCs[97] and the latter resulting data for approximately 150 organic compounds are presented.	Crommentuijn et al. (2000)	quantitative	threshold
An environmental concentration (Polycyclic aromatic hydrocarbons in surface sediments) is measured. The environmental concentration is assumed to be negligible if its risk quotient of negligible concentrations (RQ_{NCs}) is < 1 (Kalf et al., 1997).	Dauner et al. (2018)	quantitative	threshold
An environmental concentration (ammonium in soil) is measured. The environmental concentration is assumed to be negligible for multiple reasons: It was very small and in some cases it was lower than a limit of detection.	Davenport et al. (2012)	quantitative	limit of detection
An environmental concentration (elemental carbon in air) is measured. Without providing a specific cutoff value, the environmental concentration is assumed to be non-negligible due to not being very small.	Decesari et al. (2010)	quantitative	value
An environmental concentration (active substances of PPPs[98] and transformation products of these active substances from protected crops) is measured.	EFSA (2014a)	quantitative	threshold
An environmental concentration (levoglucosan in the Atlantic Ocean) is measured. Without providing a specific cutoff value, the environmental concentration is assumed to be negligible due to being very small.	Häggi et al. (2021)	quantitative	effect level
An environmental concentration (nitrate and sulfate in groundwater) is measured. Without providing a specific cutoff value, the environmental concentration is assumed to be negligible due to being very small.	Humez et al. (2016)	quantitative	value

[96] Maximum Permissible Concentration

[97] Negligible Concentration

[98] plant protection products

Description of methods	Source	Type	Definition
An environmental concentration (Polycyclic aromatic hydrocarbons) is measured. The environmental concentration is assumed to be negligible if its risk quotient of negligible concentrations (RQ_{NCs}) is < 1.	Kalf et al. (1997)	quantitative	threshold
An environmental concentration (nitrate and sulfate in groundwater) is measured. Without providing a specific cutoff value, the environmental concentration is assumed to be negligible due to being very small.	Kandji et al. (2017)	quantitative	value
An environmental concentration (flame retardants in potable water) is measured. Without providing a specific cutoff value, the environmental concentration is assumed to be negligible due to being lower than the limit of detection.	Khan et al. (2016)	quantitative	limit of detection
An environmental concentration (Polycyclic aromatic hydrocarbons in a river) is measured. The environmental concentration is assumed to be negligible if its risk quotient of negligible concentrations (RQ_{NCs}) is < 1 (Kalf et al., 1997).	R. Li et al. (2019)	quantitative	threshold
An environmental concentration (gypsum in the surface mineral horizon) is measured. The environmental concentration is assumed to be negligible if <30 $mg \cdot g^{-1}$, although the origin of this cutoff value is neither explained nor justified.	Olarieta et al. (2016)	quantitative	value
An environmental concentration (heavy metals in wastewater) is measured. The environmental concentration is assumed to be negligible due to being smaller than multiple official thresholds, namely those established by the Indonesian Ministry of Environment (KEPMENLH), the World Bank, and the World Health Organization (WHO).	Rosyida et al. (2022)	quantitative	threshold
An environmental concentration (phosphorus in soil) was measured. The environmental concentration is assumed to be negligible as it is beneath a threshold published in other literature (Heckrath et al. 1995; Hooda et al. 2000).	Sigua et al. (2010)	quantitative	threshold
An environmental concentration (toxic metals in EAF[99] slag) is measured. The environmental concentration is deemed negligible due to being lower than multiple official thresholds, specifically those set by the Indian Standard (IS 383:2016) and the Environmental Protection Agency (EPA).	Singh et al. (2021)	quantitative	threshold
An environmental concentration (Polycyclic aromatic hydrocarbons in a river) is measured. The environmental concentration is considered to be negligible if both its risk quotient of negligible concentrations (RQ_{NCs}) and the risk quotient of maximum permissible concentrations (RQ_{MPCs}) are significantly lower than 800 and 1 respectively (Kalf et al., 1997).	Zhang et al. (2018)	quantitative	threshold

[99] Electric arc furnace

B.2 Methods in context of "exposure"

Description of methods	Source	Type	Definition
A risk/probability of exposure (microplastic) is calculated. It is the probability that the exposure concentration is higher than a self-estimated exposure concentration threshold ("safe concentration"), which they estimated.	Beiras and Schönemann (2020)	quantitative	probability
An exposure concentration (Mercury concentration in forage plants) is measured. Without providing a specific cutoff value, the exposure concentration is assumed to be negligible due to being very small.	Bergman and Bump (2014)	quantitative	value
Determinants for environmental exposure assessment are given. Environmental exposure is considered to be not negligible, if the PEC[100] exceeds the threshold.	ECHA (2016)	quantitative	threshold
An effect assessment schemes on pesticides was carried out for aquatic organisms in edge-of-field surface waters. The assessment schemes allow for the derivation of regulatory acceptable concentrations (RACs) on the basis of two options: (1) the ecological threshold option (ETO), accepting negligible population effects only, and (2) the ecological recovery option (ERO), accepting some population-level effects if ecological recovery takes place within an acceptable time period.	EFSA (2013b)	quantitative	threshold
A risk assessment was carried out on a pesticide (triflusulfuron-methyl). An exposure concentration is measured. The exposure concentration is assumed not to be negligible when the PECgw for metabolites IN-E7710, IN-M7222, IN-W6725 and IN-JU122 are > 0.1 µg/L in all relevant FOCUS scenarios.	EFSA (2022a)	quantitative	threshold
A risk assessment was carried out on a pesticide (dimethomorph). Using FOCUS methods rates of dissipation and degradation in the environmental matrices, groundwater scenarios, low acute and chronic risk to different species were investigated. Ecotoxicology assesment was based on regulatory documents (European Commission, SETAC[101], EFSA[102] and EFSA PPR[103] Panel).	EFSA (2023a)	quantitative	threshold
A risk assessment was carried out on a pesticide (metiram). Using FOCUS methods rates of dissipation and degradation in the environmental matrices, groundwater scenarios, low acute and chronic risk to different species were investigated.	EFSA (2023b)	quantitative	threshold
Average Effects (leaf damage in greenhouse tomatoes) with and without the "negligible" exposure concentration (0.5 mg/L NaCl[104] in irrigation water) were measured and compared. Regardless of the comparison results,	Guidi et al. (2011)	quantitative	value

[100] predicted environmental concentration

[101] Society of Environmental Toxicology and Chemistry

[102] European Food Safety Authority

[103] Panel on Plant Protection Products and their Residues

[104] sodium chloride

Description of methods	Source	Type	Definition
the exposure concentration of 0.5 mg/L NaCl was initially referred to as "negligible" without specifying a cutoff value to determine what qualifies as "negligible".			
An exposure concentration (silicone (Si) and lead (Pb) in erythrocytes of fish) is measured. Without providing a specific cutoff value, the exposure concentration is assumed to be negligible due to being very small.	Massar et al. (2012)	quantitative	limit of detection
An exposure concentration (cadmium in seeds) is measured. The exposure concentration is assumed to be negligible for multiple reasons: It was very small, it was lower than a WHO[105] threshold and in some cases case it was lower than a limit of detection.	Prapagdee and Khonsue (2015)	quantitative	value
An environmental concentration (Mycotoxin) is measured. The environmental concentration is assumed to be negligible because it was small compared to a legal threshold.	Santis et al. (2021)	quantitative	threshold
An exposure concentration (Chromium contamination for different crops) was measured. The exposure concentration was found to be negligible for *Zea mays* because it is much lower compared to that of the other crops.	Shams et al. (2010)	quantitative	value
Average Effects (survival of rainbow trout) with and without the "minor" exposure concentration (1 mg/mL Oxytetracycline in the water) were measured and compared. Regardless of the comparison results, the exposure concentration of 1 mg/mL Oxytetracycline was initially referred to as "minor" without specifying a cutoff value to determine what qualifies as "minor".	Sundberg and Karvonen (2018)	quantitative	value

B.3 Methods in context of "effect"

Description of methods	Source	Type	Definition
(1) The occurrence of an effect (guttation of beets) is counted at multiple sites. The exposure is assumed to be negligible if the effect occurs in <10% of all sites. (2) A risk/exposure is assumed to be negligible if the effect (daily mortality) increases more than 1.5 times compared to controls for six days. (3) An effect (reduction in colony size) is assumed to be negligible if its decrease is between 3.5% and 7%.	EFSA (2013a)	quantitative	threshold

[105] World Health Organization

Description of methods	Source	Type	Definition
(4) An exposure is assumed to be negligible if the 90th percentile of its estimates does not exceed the NOEL[106] threshold.			
An effect (reduction in colony size) is assumed to be acceptable if it lies within the background variability of the control.	EFSA (2020)	quantitative	benchmark
An effect assessment schemes on pesticides was carried out for Non-Target Terrestrial Organisms by the concepts of Effect Assessment Goal (EfAG) and Exposure Assessment Goal (ExAG).	EFSA (2022c)	quantitative	description
An effect assessment schemes on pesticides was carried out for birds and mammals by the concepts of Effect Assessment Goal (EfAG) and Exposure Assessment Goal (ExAG).	EFSA (2023d)	quantitative	benchmark
An effect is assumed to be negligible if the difference in the sublethal effects between treatment and control is ≤ 10%.	EFSA (2023c)	quantitative	threshold
An effect (reactivity of certain volatile organic compounds to contribute to ozone formation) is measured. Without providing a specific cutoff value, the effect is assumed to be negligible due to being very small.	EPA (1977)	quantitative	benchmark
An effect (reactivity of certain volatile organic compounds to contribute to ozone formation) is considered negligible if it is equal to or smaller than the reactivity of ethane, i.e. a Control.	EPA (2005)	quantitative	benchmark
Average Effects (ability of Hg[107] removal by marine macroalgae) with and without the exposure (presence of potentially toxic elements) were measured and compared. The effect of the substance was found to be negligible since the p-value of the statistical test for the comparison was > 0.05.	Fabre et al. (2020)	quantitative	threshold statistical
An effect (toxicity against larvae of non-target organisms) of an exposure (*M. sylvestris* aqueous extract and green-synthesized silver nanoparticles AgNP) is assumed to be negligible, if mortality does not increase until 48h after the exposure to 50 times the LC_{50}[108] dose for target organisms.	Govindarajan et al. (2016)	quantitative	value
Average Effects (abundance of ants and springtails) with and without the exposure (herbicide applied to wheat field) were measured and compared. Albeit p-values < 0.05, the effect of the substance was found to be negligible, since the comparison of the second effect (tillage) resulted in larger differences.	Greenslade et al. (2010)	qualitative	description
An effect (Persistent Organic Pollutants in tissue) of an exposure (ingestion of plastic) was measured. The effect is assumed to be negligible since the effect of another exposure (ingestion of natural prey) is larger.	Herzke et al. (2016)	quantitative	value

[106] No Observed Effect Level

[107] mercury

[108] median lethal dose

Description of methods	Source	Type	Definition
An effect (carbon footprint of households) was measured and compared to the same effect for previous years, assuming that exposure may have changed. The effect is assumed to be negligible as it is comparable to that of previous years.	Long et al. (2021)	quantitative	benchmark
Average Effects (bee colony growth) with and without the exposure (pesticide) were measured and compared. The effect of the exposure was found to be negligible since the p-value of the statistical test for the comparison was > 0.05.	Payne et al. (2019)	quantitative	threshold statistical
A risk/probability of exposure is assessed. The risk is assumed to be negligible if it falls within a triangular distribution with a most probable value of zero and a maximum value of one in a million, i.e. it's likelihood is less that $10^{-6.}$	Powell (2013)	quantitative	probability
Average Effects (reproductive or offspring developmental parameters in zebrafish) with and without the exposure (polystyrene microplastics) were measured and compared. The effect of the exposure was found to be negligible since the p-value of the statistical test for the comparison was > 0.05.	Qiang et al. (2020)	quantitative	threshold statistical
Average Effects (mortality and oxidative stress status parameters in *Tubifex tubifex*) with and without the exposure (polyethylene microplastics) were measured and compared. The effect of the exposure was found to be negligible since the p-value of the statistical test for the comparison was > 0.05.	Scopetani et al. (2020)	quantitative	threshold statistical
Summarized in chapter 3.3.2. Key Publications	Weltje et al. (2013)	qualitative	description
Average Effects (thiacloprid dissipation and enzyme activities in the soil) with and without the exposure (microplastic type and size) were measured and compared. The effect of the exposure was found to be negligible since the p-value of the statistical test for the comparison was > 0.05.	Xu et al. (2020)	quantitative	threshold statistical