INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

GUIDELINE FOR EXTRACTABLES AND LEACHABLES Q3E

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ICH Q3E
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GUIDELINE FOR EXTRACTABLES AND LEACHABLES

Q3E

ICH Consensus Guideline

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1. INTRODUCTION

Leachables are chemical entities that migrate from manufacturing components/systems, packaging or delivery device components into a drug product under the established manufacturing and labelled storage conditions. Extractables are chemical entities that are intentionally extracted from manufacturing components/systems, packaging or delivery device components under specified laboratory test conditions and thus are potential leachables.

This guideline presents a holistic framework and process for the assessment and control of leachable impurities to further expand the existing ICH guidelines on impurities, including impurities in new drug substances (ICH Q3A) and new drug products (ICH Q3B), residual solvents (ICH Q3C), and elemental impurities (ICH Q3D), as well as DNA reactive (mutagenic) impurities (ICH M7). The framework of this guideline follows the principles of risk management as described in ICH Q9. While the guideline includes materials characterization and process understanding, its primary purpose is to protect patient safety and product quality through assessment and control of leachables in the drug product. Due to rapid advances in materials engineering, device innovations, new manufacturing paradigms and novel therapeutic modalities, the aim is to provide principles and concepts that are forward looking within the scientific and regulatory landscape.

2. SCOPE

The guideline applies to the risk assessment and control of leachables in new drug products, including cell and gene therapy products. Drug-device combination products that require marketing authorizations and meet the definition of pharmaceutical or biological products are also in scope.

Organic leachables are the primary focus of this guideline. Though recommended methodologies for elemental analysis are within the scope of this guideline, the safety assessment of elemental leachables are addressed by ICH Q3D and thus out of scope for this guideline.

The guideline also applies to approved products for any changes that are likely to impact the leachable profile or patient exposure such as those relating to formulation, manufacturing, dosing, and/or container closure system (i.e., life cycle management). This guideline is not intended to apply to extrinsic, extraneous or foreign substances resulting from product contamination or adulteration.

This guideline is not intended for herbal medicinal products and crude non-processed products of animal or plant origin. For these products in liquid dosage forms, regional expectations may apply.

This guideline is not intended for products used during clinical research stages of development. However, in cases of high risk to the patient, principles of this guideline may be applicable to support clinical studies.

Generally, radiopharmaceuticals are not considered in scope, unless there is a specific cause for concern.

The guideline does not apply to systems used in the manufacture or storage of excipients. Refer to Section 3.4.1 for special considerations regarding packaging components for liquid or semiliquid active pharmaceutical ingredients (APIs).

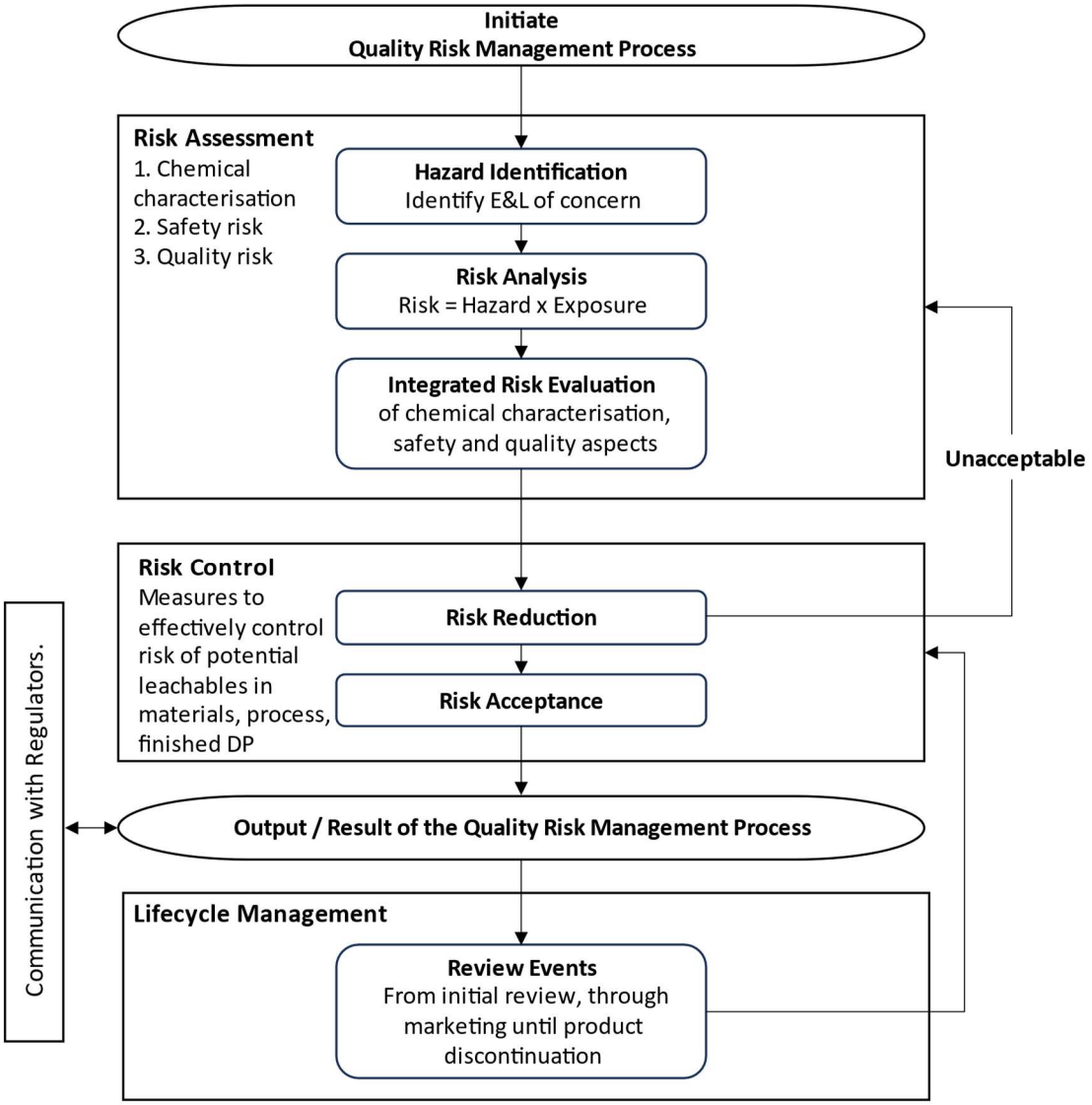
3. RISK ASSESSMENT AND CONTROL OF EXTRACTABLES AND LEACHABLES

3.1 General Principles

The purpose of the guideline is to provide a holistic framework whereby leachables-associated risk can be identified, assessed, and controlled to protect the safety, efficacy, and quality attributes of the finished drug product. Figure 1 is intended to inform product development considerations leading up to product registration as well as continuous quality management process throughout lifecycle management.

Figure 1: Overview of the Risk Management Process

(E&L = Extractables and Leachables)



The quality risk management process for E&L warrants a holistic strategy, leveraging prior knowledge and a thorough understanding of the desirable and critical attributes for the manufacturing/packaging components and drug product, as well as the manufacturing and storage conditions. Close collaboration between the analytical chemist(s) and safety expert(s) is essential for knowledge sharing and development of the E&L quality risk management process. A Quality Risk Management Process should be initiated with every product, each with its own Risk Assessment, Risk Control and Lifecycle Management process.

3.2 Risk Matrix as a Multifactorial Concept

For the overall risk assessment and control of leachables, it is important to consider the multidimensional nature of risk, entailing both pharmaceutical quality and safety aspects. With respect to pharmaceutical quality, important dimensions include:

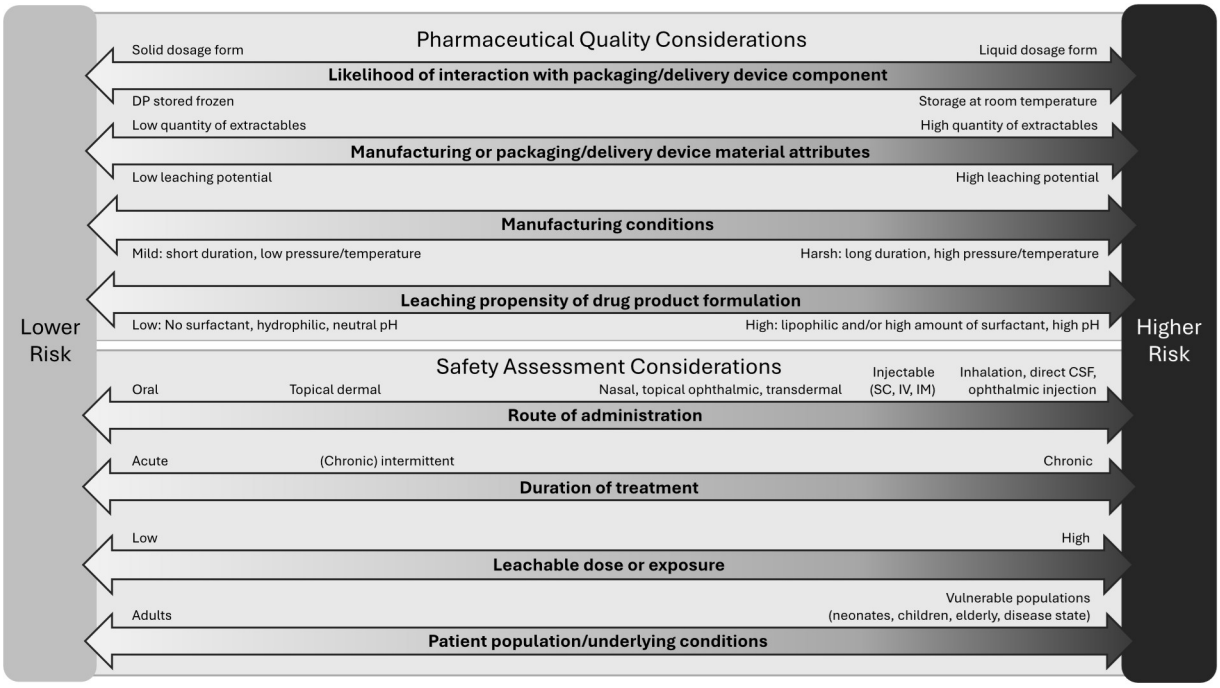
- The potential for interaction between manufacturing equipment or packaging component and the formulation,
- The chemical and physical properties of the equipment or component that likely contribute to leachables, and pre-treatment of components prior to use,
- The manufacturing and storage conditions, including but not limited to, surface area to solution volume ratio, temperature, duration of contact, proximity of the downstream removal steps and their capacity to deplete potential leachables.
- The leaching propensity of the formulation, including but not limited to API, pH, organic co-solvents and surfactant/chelating agents.

Safety assessment dimensions relate to the potential harms posed by leachables, inclusive of exposure-related factors such as the risk impact of the route(s) of administration, pertinent patient population(s), maximal dosing, dosing frequency and/or intervals, and maximum potential treatment duration in a lifetime.

The relative risks associated with various dimensions (not all inclusive) are shown in Figure 2. The overall risk of a drug product is determined by taking all those dimensions into consideration.

Figure 2: Overview on Aspects to Consider for Risk Matrix

CSF = Cerebrospinal fluid; DP = Drug product; IM = Intramuscular; IV = Intravenous; SC = Subcutaneous



Depending on the anticipated risk and leveraging prior knowledge, various approaches can be adopted ranging from compliance with relevant food-contact safety or pharmacopeial standards/regulations to more extensive E&L characterization and safety risk assessment (See Appendix 1). For oral drug products, compliance with relevant regional food-contact safety regulations may be sufficient to support the safety and quality of polymeric manufacturing equipment/systems and container closure systems if adequately justified (e.g., proposed use is consistent with regional regulations for food contact use, the leaching propensity of the drug product is similar or less than those listed in a referenced regional regulation, and all specified testing results meet acceptance criteria). For all other drug products, or for oral products that do not comply with the regulations for food contact in terms of composition, specification, and in-use limitations, extractable/leachable assessments are typically warranted.

The risk matrix and factors described above highlight the complexity of the risks associated with a leachables assessment. Understanding the respective risk level of the corresponding factors is part of the risk assessment process and may inform manufacturing and packaging components selection as well as the development of an overall risk assessment/control strategy.

3.3 Risk Assessment

Based on the descriptions of the Risk Management Process (Figure 1, Section 3.1), the Multidimensional Risk Matrix (Figure 2, Section 3.2) and the Typical Workflows for E&L risk assessment and risk control (Figures 4 and 5, Appendix 1) risk assessment can be summarized in three basic steps:

- Step 1 - Hazard Identification: Identify potential leachables that may migrate into the drug product from direct (e.g., manufacturing components/systems, container/closure systems and delivery devices components) or indirect (e.g., secondary packaging, ink or adhesives on labels particularly for semi-permeable components) contact surfaces based upon prior knowledge (experience with component, prior testing, etc.) and/or extractables and leachables testing.

- Step 2 - Risk Analysis: Quantitate the potential occurrence of leachables in the drug product and assess the patient exposure to leachables.

- Step 3 – Integrated Risk Evaluation: Evaluate the potential risk to impact product quality, safety and efficacy to determine if the selected manufacturing components/systems and container/closure systems are considered qualified for the intended use.

3.4 Risk Control

If the comprehensive risk assessment indicates risk mitigation is needed, measures may include, but are not limited to, change of components/suppliers, pre-wash of components, pre-flushing of manufacturing equipment, and adding additional purification/isolation step(s). The adequacy of the mitigation measures ultimately implemented should be confirmed/verified via extractable and/or leachable studies.

Once the components are qualified for the intended use, a control strategy should be implemented. This comprises, but is not limited, to routine GMP practices which are imperative for component quality controls. A control strategy should be in place to:

- Establish adequate acceptance quality control including acceptance criteria, analytical procedures, and sampling plan for components as appropriate.

- Establish appropriate quality agreement with component venders including component

lifecycle quality controls regarding any composition and/or fabrication process changes that might have impact on the extractable profiles.

See Appendix 1 for typical workflows for E&L risk assessment and risk control, including component qualifications for manufacturing components/systems (Figure 4, Appendix 1) and for packaging and delivery device components (Figure 5, Appendix 1). Typically, extractable and leachable studies should be conducted for packaging and delivery device components. Under certain circumstances alternative approaches may be proposed with proper justifications.

The principles and practices used for identifying risk and developing mitigation strategies to address safety concerns associated with packaging and delivery device components are also applicable to formulation contacting manufacturing equipment components made of polymeric materials. Extractables studies should therefore be designed to represent the worst-case scenario of the manufacturing conditions (e.g., smallest scale with longest contact durations, highest temperature and pressure). It is recognized that the potential for leachables in a drug product originating from the manufacturing components/systems is lower than that from the packaging and delivery components, due to relatively shorter contacting time with the formulation and larger solution volume to surface area ratio. Leachables introduced in upstream manufacturing process steps might be able to be purged through downstream steps, e.g. purification/polish, lowering the risk for leachables ending up in the final drug product. These factors should be taken into consideration for manufacturing equipment selection and qualification, as well as quality investigations.

For manufacturing components/systems, the leachables risk may be considered minimal and acceptable when all extractables peaks are at or below the Analytical Evaluation Threshold (AET) applicable to the drug product and no Class 1 leachables are observed (see Section 5). The analytical procedures used in extraction studies should comply with the criteria provided in Section 4.3.

In cases where manufacturing components/systems extractables are observed in concentrations above the AET, an identification of those extractables and quantification of the concentrations may be conducted to mitigate the leachables risk as long as the quantification of extractables is performed against appropriate reference standards of the same identity as the identified extractables. However, if authentic reference standards do not exist, compounds with a similar

analytical response can be employed. If extractables concentrations quantified in this manner are below the relevant acceptable safety level (see Section 6), then the safety concern associated with leachables risk is considered negligible. As an alternative to qualification of extractables from manufacturing equipment at concentrations above the AET, a safety assessment of leachables may be performed.

For a packaging component/system an abbreviated data package may be considered when patient safety risk can be adequately mitigated by prior knowledge, (e.g. established extractable/leachable correlation, similar drug product with similar leaching propensity to approved drug product formulation), or no/few extractables detected above the AET and below their applicable safety threshold (such as Class 3 leachables; See Section 6). Table A.1.2 (Appendix 1) provides examples where the overall risk is considered low, in relation to Figure 2 (Section 3.2), and an abbreviated data package may be warranted with adequate justification. When an abbreviated data package is proposed, communications with relevant regional Regulatory Agency/Health Authority is recommended to align on approach.

If identified extractables are likely to chemically transform into compounds with a higher safety risk (i.e. through chemical degradation and/or interaction with formulation components to generate compounds with a higher safety risk), or if not all extractable peaks above the applicable AET can be adequately identified and/or quantified, a leachable study should be conducted to address these concerns and demonstrate acceptability of the components.

3.4.1 Special Considerations

When multiple manufacturing components, especially those constructed with the same or similar material are used, the cumulative leachables risk should be assessed.

Quality risk assessment and derived control strategies, when appropriate, should also encompass potential leachables from a container used to store a liquid or semi-solid drug substance.

Although minimal leaching occurs in the frozen state, the potential for leaching from storage component/system should be evaluated before freezing and after thawing.

In addition, for biological and biotechnology-derived products risk identification and mitigation may also include:

- Evaluation of the potential interactions between reactive leachables and formulation components that may lead to potentially adverse impact on product quality, safety, and/or efficacy. If impacts to critical quality attributes of the product by known reactive leachables are identified, potential mechanisms of chemical modification should be considered (such as denaturation, aggregation or degradation).

- For manufacturing of drug substance, leachables may be removed during the last purification step. Therefore, the quality risk assessment will typically focus on subsequent manufacturing processes.

3.5 Documentation and Compliance

Registration applications should include the justification for the extractable/leachable studies conducted, the associated study reports, the safety assessment of substances above the AET and any requisite risk control strategy. Extractables and leachables studies conducted to support the acceptability of manufacturing and packaging components/systems should be included in filing submissions (as described in ICH M4Q) as applicable. Adequate leachable data should be provided to address safety and quality concerns throughout the drug product's shelf life. It is generally acceptable to submit leachable study results aligned with available stability data, with the provision to submit additional data post-authorization, subject to prior concurrence with the relevant regional regulatory authority. The quality risk assessment as defined in Section 3.3 of this guidance should be conducted on single-use and multi-use manufacturing components/systems, primary packaging components and delivery device components. For semi-permeable packaging materials, secondary packaging should also be evaluated as applicable.

A list of extractables and leachables studies conducted should be included along with an assessment report which will typically include analytical method and extraction condition selections along with justifications (solvents, temperature, duration, surface/volume ratio, etc.) for extractables studies and a description of the sample preparation and analytical procedures for leachables studies. In addition, the quantification procedure(s) should be described including the suitability of the procedures used for quantification (e.g., limit of detection (LOD), limit of quantification (LOQ), specificity, linearity, accuracy, and repeatability). All extractables and leachables peaks above the AET (see Section 5) should be included in the filing submission with chemical name, structure, CAS Registry Number (if available) and observed level. For leachables (or extractables when such testing is used for qualification),

safety risk assessment as described in Section 6 should be included.

In addition to the quality risk assessment, a leachables to extractables correlation should be included in the registration application, as appropriate (refer to Section 4.6). Finally, the adequacy of any proposed mitigation measures (for example prewashing of the packaging and delivery components/system or pre-flushing of the manufacturing components/systems) should be demonstrated by data collected before and after implementation.

3.6 Risk Review / Lifecyle Management

This section describes the types of changes that might necessitate re-evaluation of the leachable profile during the lifecycle of the drug. The following is a non-exhaustive list of potential changes and an explanation of how these represent a potential to impact the patient leachable exposure. As such, these changes should be considered and justified scientifically using new studies and/or existing information sources.

New Information: If new data and/or information on a material pertinent to its suitability for use indicates a cause for concern and/or if new patient safety information for a leachable becomes available, an updated assessment may be warranted.

Changes to a drug product formulation: Changes to the drug product may cause different leachables from the existing formulation contacting manufacturing components/systems and/or primary packaging and/or delivery device components. For example, changes to excipients/surfactants composition or concentrations can affect both the composition and amount of leachables.

Changes to container closure system, delivery device, or manufacturing components/systems that contact drug substance and/or drug product: When there are known changes such as the composition, supplier, manufacturing process, geometry or pretreatment of materials contacting the drug substance (mainly for liquids and/or biologics) or drug product during the shelf-life of the drug, there is a potential for an altered leachable profile. In addition, for some products there may be a potential for non-direct packaging components to contribute potential leachables to the drug product.

Changes to a manufacturing process: Changes to process conditions may cause different leachables or different amounts of leachables from the existing formulation contact material. For example, change in solvent system, duration, temperature, pressure, pH,

cleaning/sterilization process, surface area/volume ratio, pre-operation preparation (e.g., flushing), amongst others can affect both the composition and amount of leachables.

Changes that might affect patient exposure: Changes such as the posology of the drug, duration of treatment, route of administration and patient population (i.e., geriatric/pediatric) have the potential to change estimates of patient exposure to previously identified leachables, which may all affect the fundamental assumptions made in the exposure assessment and toxicological risk assessment of leachables.

Changes in indication that might affect patient benefit:risk: e.g. oncology to rheumatological disorders.

4. CHEMICAL TESTING AND ASSESSMENT

4.1 Prior Knowledge

Prior knowledge may comprise information useful to obtain before performing chemical testing, including information available from a supplier and any relevant information with regard to other drug products and processes. This information may include:

- composition (e.g., base polymer and copolymer, any known additives such as plasticizers, processing aids, catalysts, antioxidants)
- food contact compliance
- statements indicating particular (e.g., non-authorized) compounds have not been intentionally added
- compendial testing
- any available extractables studies
- biological reactivity testing
- processing or pretreatment steps (e.g., sterilization, cleaning, flushing, siliconization, surface treatments)
- prior use history, including any historical use with other similar drug products, process and/or contact conditions

4.2 Component Selection

A pharmaceutical product manufacturer is responsible for establishing requirements in

alignment with regulatory expectations for the manufacturing, packaging, storage, and delivery of a unique drug product safely and effectively to an intended patient population. The level of risk for a particular material or component is relevant to the potential for interaction with the dosage form. For example, components that interact with dosage forms exhibiting a greater propensity for leaching (e.g., liquids) may be considered of higher risk than components that interact with dosage forms which exhibit a minimal propensity for leaching (e.g., non-lyophilized solids). The information obtained from the supplier (e.g., extractables report, compliance with compendial requirements) may be supplemented with additional testing appropriate for conducting a risk assessment and developing extractables/leachables procedures to demonstrate acceptable component selection. See Table A.2.1 (in Appendix 2) for a summary of extractable, leachable and simulated leachable studies.

4.3 Extractable Study

An extractable study is a process by which chemical entities are extracted from a test article. An adequate extractables study incorporates solvents and extraction conditions relevant to the anticipated leaching propensity of the drug product formulation under the worst-case scenario of manufacturing or storage conditions and employs multiple complementary analytical techniques to establish a comprehensive extractables profile. Key characteristics of an adequate extraction study include:

- Establishment and application of a drug product-specific AET to indicate extractable chemical entities to be identified and treated as potential leachables. Testing is performed on components or an assembled system including any processing and treatment (e.g., sterilization, molding and fabrication conditions, cleaning, siliconization) that would be representative of the final, finished component or system as intended for use

- Proper extraction media selection, including appropriate solvents of varying pH and polarity relevant to and representative of the drug product formulation (e.g. excipients, surfactants)

- Represents the drug product specific worst-case scenario for leachables occurring during manufacturing or arising from packaging components/systems during shelf life (e.g., contact area, temperature, duration)

- The analytical procedures used are adequately qualified at a level commensurate with

the purpose of the extraction study

- Includes appropriate analytical procedures for volatile, semi-volatile, and non-volatile organic extractables and elemental extractables

- The extractables report describes details on analytical procedures

Specific targeted tests for potential Class 1 leachables (see Section 6.2 Leachables Classification) should be performed based on the understanding of the material of construction and quality; risk analysis should be performed as appropriate. Analysis of potential Class 1 leachables should follow the description of a quantitative extractables study (Section 4.3.2) or leachables study (Section 4.4).

4.3.1 Semi-Quantitative Extractables Study

A semi-quantitative extractables study may be appropriate in scenarios where a leachables study will subsequently be conducted to establish the acceptability of materials for intended use. The purpose of a semi-quantitative extractables study is to understand which extractables can be present as leachables in the drug product. Key characteristics of the semi-quantitative extractables study include:

- Analytical procedures that are qualified using several relevant standard compounds typically observed as extractables or leachables.

- Use of analytical uncertainty factor (UF; Section 5.1) in the calculation of the drug product-specific AET.

- Quantification of observed extractables against relevant standard compounds.

Semi-quantitative extractables observed above the AET can subsequently be used as targets for a quantitative extractables study or a leachables study.

4.3.2 Quantitative Extractables Study

To support qualification of manufacturing components/systems and certain low-risk packaging components/systems scenarios (Refer to Appendix 1 Table A.1.1 and A.1.2, respectively) for which extractables were observed at a level above the AET during the semi-quantitative extractables study, a quantitative extractables study to quantify these specific extractables would be warranted. Key characteristics of quantitative extractables study include:

- Confirmed identification of extractables above the AET.

- Quantification of the identified extractables above the AET using standards with identical or similar analytical response.

- The analytical procedure used for quantifying the identified extractables above the AET should be qualified for the specific standard compound.

If the amount of an adequately identified and quantified extractable exceeds its qualification limit (e.g., applicable safety threshold or permitted daily exposure (PDE)), a leachables study is warranted to demonstrate the compound as a leachable remains below its qualification limit. In addition, a leachables study can also be used to assess the quality risk for extractables above the AET when those extractables cannot be identified with confirmed identities.

4.4 Leachables Study

Leachables studies intended to support drug product registration are designed to represent the actual manufacturing conditions and intended storage conditions throughout the proposed shelf-life and in-use period. During the shelf life and in-use period, multiple time points should be evaluated to characterize trending of leachables to estimate maximal occurrence. The leachables assessment for the container closure system is performed on the actual drug product during stability storage and may include accelerated storage conditions. For a container closure system, the study should involve multiple primary drug product stability and/or development batches manufactured with the actual packaging and delivery system intended for use with the commercial product. If multiple batches are not available, alternative approaches may be proposed with justification. Use of the same lots of components used in extractables assessments potentially enables a more meaningful correlation between extractables and leachables. Analytical procedures for specific, targeted leachables should be appropriately validated to establish that they are sensitive, selective, accurate, and precise. Non-targeted screening procedures should also be used and employ appropriate analytical techniques to facilitate detection of any unanticipated degradation of leachables, leachables from secondary packaging, and/or interaction products. The non-targeted screening study should include the application of an AET (See Section 5) to indicate a level above which leachable chemical entities should be identified, quantified, and reported for toxicological assessment.

Reference standards, if available, are preferred as they facilitate more accurate and precise quantitation of target leachables that may be present as actual drug product leachables when

they are used to produce either proper response factors or calibration curves; in which case the analytical accuracy and precision is high.

4.5 Simulated Leachable Study

Circumstances may exist when performing a drug product leachables study is not technically feasible despite thorough due diligence which may include systematic investigation of multiple diverse sample preparation techniques coupled with highly sensitive and selective analytical methods, techniques and instrumentation. Such circumstances may include challenging detection or quantification thresholds associated with large volume parenterals (LVPs), significant analytical matrix interference inherent with complex drug product formulations, or a combination of such factors. In such situations, use of a simulation study to support actual drug product leachables evaluation may be justifiable. For example, a simulation study could be performed to augment a leachables study to accomplish the objectives that cannot be obtained by leachables testing. In the case of a challenging AET (i.e., procedure LOQ > AET), the leachables study would be performed with relevant test procedure LOQ and a simulation study would be performed to fill in the gap between the LOQ and the AET. Alternatively, a simulation study could be used to replace a leachables study when, through thorough due diligence, it is established that performing the leachables study is impractical.

It is important to recognize that, regardless of how well the simulation study is designed and executed, its outcome will likely only approximate the results of a drug product leachable study and cannot fully replicate a true leachable profile of the drug product. For example, a simulation study cannot and will not address any potential interaction between leachables and the components of the drug product formulation components.

The simulation study is a surrogate study that reveals likely true leachables that would be detected if a leachables study could have been conducted. Thus, the simulated leachables detected above the simulation study's drug product specific AET should be identified, quantified, and assessed for safety. As the goal of a simulation study is to obtain a simulated leachables profile that closely mimics the actual leachables profile generated by the drug product over its shelf-life, the simulation conditions and process used in the simulation study should closely match the drug product manufacturing/storage conditions used in a leachables study, with the intent of simulating the conditions experienced by the drug product during its manufacturing, shelf-life storage, and in-use (clinical) preparation. Furthermore, the simulation solvent should be chosen so that is has a similar propensity to leach as the drug product, and the simulated manufacturing process should be performed using worst-case conditions.

Moreover, a simulation study can be accelerated versus drug product shelf storage conditions to mimic the outcome of a leachable study over the entire drug product shelf life with shorter duration.

As the intent of the simulation study is to augment or replace a leachables study, the simulation study must meet all the quality requirements for a leachables study, including test procedure qualification. When properly justified, use of a simulation study is an alternative to the recommended practice of performing leachables studies. Thus, the intended application, justification, and qualification of a simulated leaching study for a particular drug product should be based on a scientifically sound rationale with demonstration of due diligence supported by appropriate testing and experimentation. When considering the use of a simulation study, consultation with the relevant regional Regulatory Agency prior to implementation may be warranted.

4.6 Extractable and Leachable Correlation

The main purpose for generating extractables profiles is to characterize and assist selection of components, identify potential leachables, develop methods for targeted leachables, and correlate leachables and extractables. Leachables generally represent a subset of the extractables and the concentration of each leachable is typically below that of the corresponding extractable from a well conducted extractables study.

Once the E&L profiles above AET are available, it is recommended that a qualitative and quantitative correlation between the two be evaluated. A correlation between leachables and extractables may be established when actual drug product leachables can be comparatively linked qualitatively and quantitatively with extractables from corresponding extractables studies of components or systems. Correlating leachables with extractables may support a justification for the use of routine extractables testing of components as an alternative to routine leachables testing during stability studies when appropriate for high-risk drug products, change control, and ongoing quality control. Potential explanations for leachables that were not detected or detected at higher levels than suggested by the extraction study conditions could include inadequate design and/or execution of the extractables study, degradation of leachables to form new compounds, interaction products of leachables with API and/or excipients, chemicals migrated from packaging, and/or new leachables resulting from materials change due to aging (e.g., exposure to UV light, heat, oxygen) during shelf-life storage. Though the E&L correlation is valuable and informative for the quality risk assessment and may be

leveraged for component selection and life-cycle management decisions, it is the leachables profile that ultimately drives patient safety risk evaluations and component acceptability.

Any changes occurring during the product life-cycle significantly altering the extractable/leachable profiles should prompt re-evaluation of the extractable/leachable profiles and their correlation. If a specific leachable is observed in the drug product during stability studies at a level significantly greater than anticipated from the calculated potential maximum level of the leachable as established with the extraction study conducted on the same component/system lots as were used for the drug product stability batches, it can indicate that the extraction study was incomplete and it may not be possible to establish a meaningful leachables to extractables correlation for that particular leachable.

5. ANALYTICAL EVALUATION THRESHOLD

The AET is not a control threshold, but rather a threshold corresponding to a concentration above which extractables or leachables should be identified, quantitated, and reported for safety assessment, forming the foundation of the overall E&L risk assessment and control strategy. The ICH guidelines on impurities in new drug substances (ICH Q3A) and impurities in new drug products (ICH Q3B), describe a series of predetermined thresholds based upon maximum daily dosing that are intended to provide adequate control over critical quality attributes that may impact the safety and efficacy of the drug product over the course of the product shelf-life. In contrast, this guideline recommends incorporation of a Safety Concern Threshold (SCT; see Section 6 Safety Assessment) to first establish a study-specific AET.

An extraction study should include the establishment and application of an AET to indicate extractable chemical entities to be detected, identified and reported as potential leachables for the drug product. For a leachable study, the AET is established at a concentration above which compounds should be identified and quantitated to enable appropriate safety assessment. For Class 1 leachables (See Appendix 4, Table A.4.1), the compound-specific safety limit, instead of a product-specific SCT, should be used for quantification.

Derivation of the study-specific AET depends on dosing considerations (e.g., maximum dose level, frequency of dosing, and duration of treatment). The AET may be expressed using various units of measure depending on the type of study (extractable vs leachable) and what is being evaluated. For example, weight of extractable per weight of component material (e.g., µg/g) or weight of extractable per extraction solution volume (e.g., µg/mL) are commonly used

units for extractables in solutions. For leachables studies, weight of leachables per packaging or delivery component/system (e.g., µg/component, µg/mL, µg/g, ppm) may be used to represent the leachables AET based on the entire container closure system or set of manufacturing components. Regardless of the units used to express the AET, they will all equate to an equivalent potential patient dose for a given study. Example AET calculations are presented in Appendix 3.

5.1 Analytical Uncertainty Factor

When an AET is used in semi-quantitative analytical methods, an appropriate uncertainty factor should be applied to account for potential underestimation of analyte concentrations due to differences in response factors between analytes and the reference standard.

The determination of the appropriate magnitude for the analytical uncertainty factor(s) in a given extractable/leachable study depends on the prior knowledge and understanding of the materials of construction, the possible chemical structure of the potential extractables/leachables, the availability of the reference standards covering the range of response factors, and the limitations of the analytical methods.

Under certain circumstances an acceptable approach is to multiply an uncertainty factor (UF) of no greater than 0.5. Alternatively, an uncertainty factor can be derived from statistical analysis of appropriately constituted response factor database of relevant reference compounds. Justification of UF applied should be included in the extractable/leachable study report.

6. SAFETY ASSESSMENT

6.1 General Principles

A risk-based scientific evaluation is needed to provide confidence that any potential leachables in the drug product are at levels where they pose negligible risk to the patient. Within this overall risk-based evaluation, the focus of the safety assessment is the toxicological evaluation of leachables in the drug product exceeding a predefined SCT for that drug product. Within this context, the SCT is considered the threshold below which a leachable would have an exposure so low as to present negligible mutagenic and non-mutagenic toxicity concerns. The outcome of the safety assessment can be used to determine if levels of Class 1 leachables from a material are considered acceptable and may be used to set specifications for leachables in the drug product if needed.

Since the SCT is defined to be protective of both mutagenic and non-mutagenic effects, it must

consider both mutagenicity concerns and concerns related to alternative toxicity endpoints and is based on whichever is more limiting with respect to exposure. As such, in addition to amount of exposure, the SCT dependent on both route and duration of exposure. For mutagenicity concerns, the Threshold of Toxicological Concern (TTC) as described in ICH M7 is considered applicable. For non-mutagenic toxicity endpoints, a Qualification Threshold (QT) is used in this guideline and may be considered as a dose at which potential non-mutagenic toxic effects are negligible. Subsequently, the SCT is the lowest value of either the TTC or QT for a specific drug product, considering route and potential duration of exposure. Oral and parenteral QT values have been derived by review of approximately 330 potential leachable permitted daily exposures (PDEs). An overview of these systemic safety thresholds (expressed in µg/day) for oral, parenteral, dermal/transdermal and inhalation routes of exposure, are provided in Table 1. In addition, local toxicity thresholds for leachable concentrations in drug products for topical ophthalmic, subcutaneous/intradermal, dermal/transdermal and inhalation routes of exposure are presented. For other routes of administration, the concepts described in this guideline may be used to determine acceptable exposure levels.

513 **Table 1: Systemic and Local Toxicity Thresholds**

Systemic Toxicity Thresholds				
Exposure Duration	**Oral**		**Parenteral, Dermal/Transdermal, Inhalation**	
	TTC	**QT**	**TTC**	**QT**
> 10 years	1.5 µg/day	48 µg/day	1.5 µg/day	12 µg/day
> 1 to 10 Years	10 µg/day		10 µg/day	
> 1 Month to 1 Year	20 µg/day		20 µg/day	
≤ 1 Month	120 µg/day	136 µg/day	120 µg/day	26 µg/day

Local Toxicity Thresholds				
Topical Ophthalmic	**Subcutaneous and Intradermal**	**Dermal and Transdermal**	**Intracerebral, Intrathecal, Epidural and Intraocular**	**Inhalation**
20 ppm	50 ppm	500 ppm	Compound-specific evaluation (see Section 6.4)	5 µg/day

514 QT values for inhalation and dermal/transdermal routes have been established based upon
515 parenteral QT in lieu of available PDE values.

516 **6.2 Leachables Classification**

517 Potential leachables from various materials encompass a large variety of chemicals, and thus
518 toxicological characteristics. To provide a pragmatic, risk-based approach to leachables safety
519 assessment, certain compounds need to be controlled at levels that are lower than the
520 established qualification threshold due to their potential for highly potent toxicity. Such
521 chemicals are categorized as Class 1 leachables in the current guideline. For mutagenic
522 carcinogens, the Cohort of Concern as defined in ICH M7 and ICH M7 Class 1 impurities with
523 an AI below 1.5 µg/day are considered Class 1 leachables. Similarly, there are some
524 compounds, such as bisphenol A (BPA) or benzo(a)pyrene, that may have potent non-
525 mutagenic toxicity concerns that may theoretically be associated with a greater than negligible
526 patient safety risk at or below the drug product QT value. For such Class 1 leachables, it is
527 considered most practical to avoid the use of materials which may leach such compounds (see
528 Section 5). However, if the use of such materials or components is considered unavoidable, a
529 compound-specific safety limit for these substances should be used.

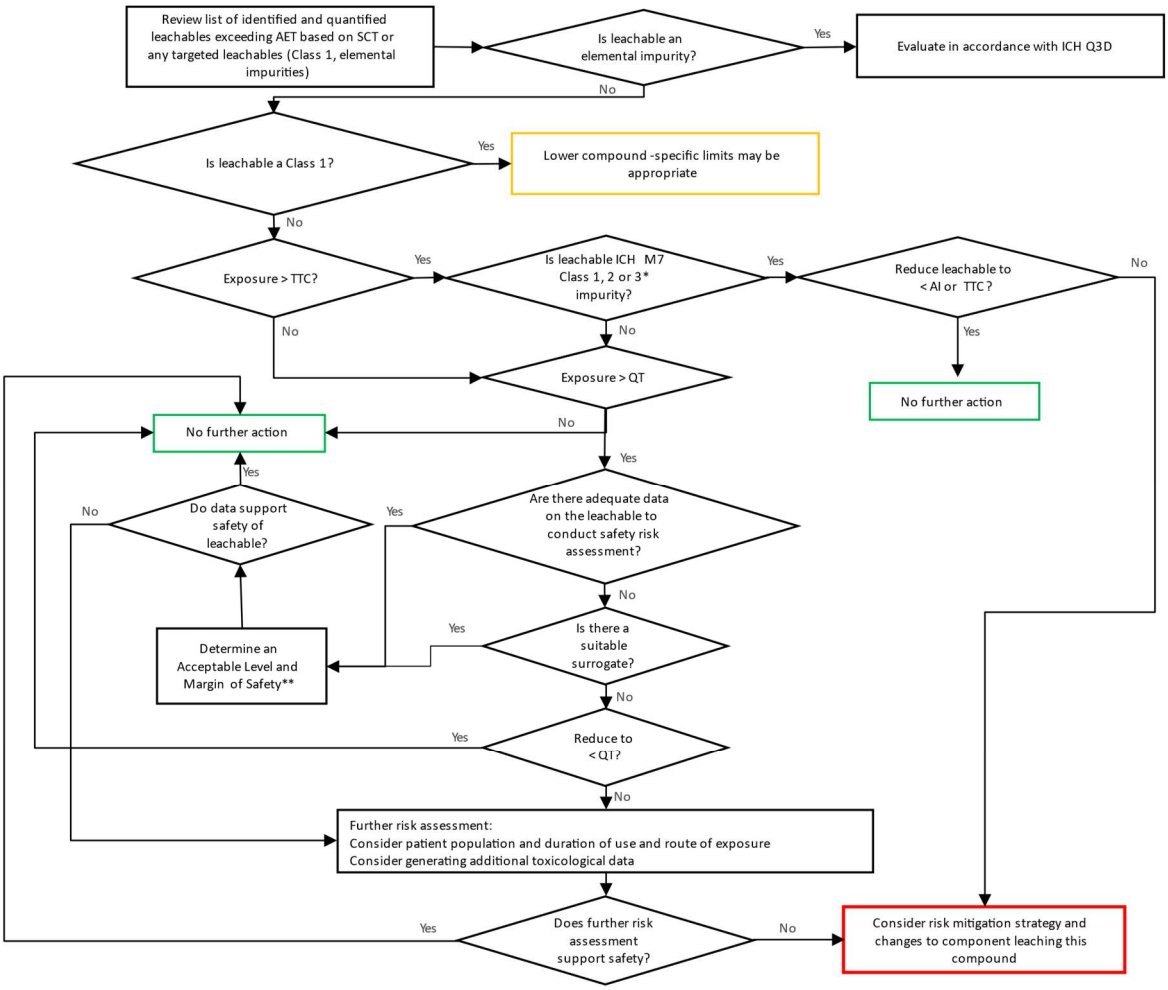
530 Class 3 leachables are compounds established to have relatively low potency for systemic
531 toxicity with derived chronic parenteral PDEs in excess of the levels at which leachables are
532 typically observed (i.e., PDE ≥ 1 mg/day using the methodology described in Appendix 5).
533 Class 3 leachables would not require further safety qualification if observed at daily exposure
534 levels < 1 mg/day. In between these two classes are compounds with a toxicity potential that

may be relevant at levels commonly encountered for leachables (Class 2 leachables). Appendix 4 provides an overview of these three leachable classes.

6.3 Safety Assessment Process

Organic leachables exceeding the AET should be identified, quantified, and reported for safety risk assessment. Acceptability of partial or incomplete elucidation of the compound structure should be justified from an analytical perspective. If toxicologically justified, partial elucidation providing tentative structures may inform a safety assessment in certain cases. The general process for safety assessment of leachables is presented in a flowchart (Figure 3) and includes an assessment of both mutagenicity and general toxicity concerns.

Figure 1: Safety Assessment Process for Leachables Using Safety Evaluation Thresholds



* As described in ICH M7.

** If daily exposure to leachable is >1 mg/day, genotoxicity studies should be considered, as recommended in ICH Q3A and ICH Q3B (e.g., bacterial mutagenicity study and *in vitro* chromosomal aberration assay).

Potential Class 1 leachables should ideally be identified and avoided during materials and component selection. However, if such compounds cannot be avoided, lower compound-specific thresholds and specifications to adequately control their presence as leachables should be implemented as an initial step in the process. Subsequently, all leachables above the TTC applicable to the drug product should be evaluated for mutagenic potential according to ICH M7. Leachables considered potentially mutagenic should be appropriately controlled within TTC limits unless de-risked by appropriate mutagenicity studies.

In addition to the mutagenicity assessment, all leachables above the applicable QT for the drug product should also be evaluated for general toxicity concerns. If adequate data are available to support the safety of the leachable at the maximal potential patient exposure, then no further toxicological assessment is needed (See Appendix 5 for further information). Conversely, if data do not sufficiently support the safety of the leachable, further action is needed to reduce the potential exposure to a known acceptable level (material replacement, etc.), generation of additional toxicological data to qualify the observed level, or a risk/benefit assessment providing justification of exposure at the observed level.

It should be noted that for leachables where adequate data to inform on the safety of the compound are not available, a read across approach using a highly similar compound(s) with toxicological data is encouraged. If suitable surrogate(s) can be identified that have sufficient data to support the safety of the observed leachable at the level observed, further safety risk assessment and/or studies can be avoided.

If the generation of novel toxicological data is considered necessary to support the safety of exposure to a leachable, New Approach Methodologies (NAMs) including *in silico* and *in vitro* models may be considered if appropriately justified. Otherwise, a toxicological qualification study(ies) as described in ICH Q3A and Q3B should be considered in order support safety assessment of the compound(s).

6.4 Route Specific Considerations and Special Cases (Local Toxicity Concerns)

Safety risk assessments for potential systemic toxicity are typically sufficient to support the safety of exposure to leachables. However, there are certain scenarios where potential local toxicity effects may be pertinent due to the potential for damage to vulnerable tissues related to the local concentration of a compound (e.g., pulmonary drug products, ophthalmic drug products, and intracerebral/intrathecal/epidural drug products). When relevant, the

toxicological risk assessment should address the potential impact of a leachable on local tissue toxicity as well as factors that may potentially reduce such concerns (e.g., formulation and excipients, contact duration, recovery of tissue damage). Additionally, when potential local toxicity needs to be considered, the SCT used should be the lowest (on a daily exposure basis) of the mutagenic (i.e., TTC), non-mutagenic (i.e., QT), and local toxicity thresholds (pertinent concentration converted to a maximum daily exposure level).

6.4.1 Ophthalmic Drug Products

Ophthalmic products are often administered topically, while some products are injected directly into ocular tissues. There is a paucity of data to characterize the potential local toxicity of leachables when in contact with ocular tissues. Based on historical precedence, in the absence of a relevant database, a compound-specific risk assessment should be completed for topically administered products to justify the safety of a leachable when it exceeds a concentration of 20 ppm in the final to-be-marketed topical ophthalmic products. This concentration limit is not considered applicable to irrigation fluids that are in transient contact with ocular tissues. For products injected into ocular tissues no threshold is given. A qualitative safety assessment of any leachables present should be provided, since such leachables may be of relevance even when present at a concentration below 20 ppm.

6.4.2 Intracerebral, Intrathecal, Epidural Drug Products

Intracerebral, intrathecal, and epidural drug products may directly interact with vital central nervous system (CNS) tissues that have a limited capacity for repair following insult, yet there is a paucity of data to characterize the potential toxicity of compounds directly administered into or in close proximity to neuronal tissue. *In vitro* data suggest chemically induced biological effects can occur in the very low parts per billion (ppb) range for some compounds with known neurotoxicity. Therefore, a compound-specific risk assessment should consider local concentration of observed leachables and the potential local toxicity concerns on neuronal tissue (e.g., neurons, astrocytes, glia, myelin) including an assessment of the potential for a local inflammatory response.

6.4.3 Dermal Drug Products

With regard to any local toxicity effects, sensitization potential (see Section 6.4.4) is likely the most sensitive non-genotoxic endpoint when the leachable concerns a strong or extreme potency skin sensitizer. For High Potency Chemicals (HPC), a Dermal Sensitization Threshold (DST) of 1 $\mu g/cm^2$/day has been derived. This threshold corresponds to 500 ppm in a dermal drug product, using the Cutaneous and Transcutaneous Concentration Limit (CTCL)

calculation for conversion as described in ICH Q3D. Consequently, a local toxicity threshold corresponding to 500 ppm concentration in the product can be used for dermal products below which there is no need for local non-mutagenic toxicity evaluation including sensitization potential (See Table 1.).

6.4.4 Sensitization Potential

Sensitizers are compounds that may trigger hypersensitivity reactions after repeated exposure. The concern for these compounds is dependent on the sensitization potential of the compound, the route of exposure and the susceptibility of the individual exposed. Different types of hypersensitivity with multiple modes of action have been described for various routes of exposure; however, validated prediction models exist for the dermal route only. This guidance addresses the risk for induction of sensitization potential and provides local toxicity thresholds for this risk where appropriate. If patients are sensitized to a compound, elicitation of sensitization reactions may occur at lower thresholds.

Dermal exposure

Most data on sensitization potential have been obtained using the dermal route. Besides human data, *in silico*, *in chemico*, *in vitro,* and *in vivo* models have been developed and used to characterize the dermal sensitization potential of compounds. DSTs have been derived based on sensitization potency.[1,2]

Where an identified leachable is administered dermally below the DST for the relevant potency category, it can be concluded that no concern for dermal sensitization is expected, and no further action is required. If the DST is exceeded, available compound-specific data on sensitization potential should be evaluated. If no such data are available, or when these data raise concerns, risk mitigation measures need to be considered. These may include replacement of the component leaching the compound or reduction of the level of the leachable.

As transdermal drugs are applied to the skin as well, the same approach can be used to evaluate the risk for sensitization potential. For multi-day patches it is assumed that all leachables migrate within a day. A slower migration rate should be justified with data.

Inhalation exposure

Knowledge of the respiratory sensitization potential of a compound is primarily from human data. Currently, suitable non-clinical models for respiratory sensitization are not established for safety risk assessment. The modes of action for dermal and respiratory sensitizers show

commonalities, but also deviate, especially after T-cell activation. Consequently, dermal sensitization data should not be used to estimate the risk for respiratory sensitization and no threshold for respiratory sensitization can be provided.

The respiratory tract is very sensitive to compounds with sensitizing (and irritating) properties[3]. Therefore, any compound with structural elements that may suggest sensitizing potential or irritation should be evaluated (e.g. isocyanates, nitriles, styrenes, short-chain aldehydes). If a compound is considered to be an irritant or have sensitizing potential, patient risk should be assessed on a case-by-case basis after evaluating the available information for the specific compound. Additionally, available clinical data should be evaluated for evidence of any adverse effects. If no concern is identified for irritancy or sensitization, a systemic toxicity QT aligned with parenteral, as presented in Table 1, is considered appropriate.

Parenteral Exposure

Regarding potential risk for sensitization, a distinction should be made between the subcutaneous/intradermal route and the intravenous/intramuscular/intraperitoneal routes of exposure. For the subcutaneous route, the drug is administered in the vicinity of the same tissues and cells (i.e., Langerhans cells) that are pivotal in triggering dermal sensitization. Especially, when the leachable is not readily distributed and remains for more extended periods in the subcutis, the same modes of action may be activated. Consequently, available data on dermal sensitization potential can be informative when evaluating the sensitization potential for leachables that are administered subcutaneously. Likewise for products administered intradermally, dermal sensitization data may be of relevance. In contrast, dermally applied compounds need to penetrate the skin barrier first. To account for this difference a ten-fold lower threshold for subcutaneous and intradermal products as compared to dermal products is considered justified, i.e., 50 ppm instead of 500 ppm.

Several types of systemic hypersensitivity (Type I-IV) are known, each having different modes of action. Type IV is dependent on hapten formation and thus shares some mechanistic aspects with dermal sensitization. However, contrary to dermal application, intramuscular and intravenous administered substances are rapidly distributed systemically, and large amounts are required to activate the immune system and induce sensitization. Since leachables are present at low concentrations in drug products, it is considered unlikely that sensitization potential will be of concern for drugs administered via intravenous or intramuscular injection.

6.5 Considerations for ICH S9 Products

For drug products within the scope of ICH S9, leachables should generally be identified according to the scientific principles outlined in Section 3 above. The safety risk assessment may be conducted according to the 'Evaluation of Impurities' Section in ICH S9. In this case, the TTC would not be applicable and the SCT would be defined by the QT. Risk assessment may be conducted with a focus on general safety for the intended patient population and is relevant for genotoxic APIs covered by ICH S9 Q&A, 2018.

6.6 Content of Safety Assessment

A safety assessment should be conducted for observed Class 1 leachables, Class 2 leachables detected at levels above the relevant SCT, and Class 3 leachables when present at levels above 1.0 mg/day. The safety assessment should provide sufficient information to conclude on the acceptability of the anticipated patient exposure levels. Further details on the information to be considered and the methodology for deriving an acceptable exposure level is provided in Appendix 5.

7. GLOSSARY

Analytical Evaluation Threshold (AET):

The threshold above which an extractable or leachable should be identified, quantified, and reported for safety assessment.

Chemical characterization:

The process of obtaining chemical information about the composition of an item such as pharmaceutical packaging and a pharmaceutical manufacturing component.

Component:

A single item, composed of one or more materials of construction, that serves a single purpose or performs a single and specific task.

Extraction:

The chemical or physical process of transferring constituents of a test article into an extraction medium.

Critical quality attribute:

A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.

Drug product:

The dosage form in the final immediate packaging intended for marketing.

Drug substance:

The unformulated active pharmaceutical ingredient that may subsequently be formulated with excipients to produce the dosage form (or drug product).

Extractables Profile:

Qualitative or semi-quantitative/quantitative accounting of the extractables present in an extract.

Leachables Profile:

Qualitative and/or quantitative accounting of the leachables present in a drug product.

Lifecycle:

All phases in the life of a product from the initial development through marketing until the product's discontinuation

Lowest-Observed (Adverse) Effect Level (LO(A)EL):

The lowest dose of substance in a study or group of studies that produces biologically significant increases in frequency or severity of any (adverse) effects in the exposed humans or animals.

Read-across:

A technique for predicting endpoint information for one substance by using data from the same endpoint from (an)other structurally-related substance(s).

Margin of Safety:

A correlation between the PDE of the specific leachable and actual patient intake based on the daily dose.

Materials of construction:

Individual materials used to construct a packaging or manufacturing component or system.

New drug product:

A pharmaceutical product type, for example, tablet, capsule, solution, cream, which has not previously been registered in a region or Member State, and which contains a drug ingredient generally, but not necessarily, in association with excipients.

No Observed (Adverse) Effect Level (NO(A)EL):

The highest concentration or amount of a leachable or extractable that does not cause any statistically or biologically significant (adverse) effects in the exposed population compared to a control group.

Permitted Daily Exposure (PDE):

The maximum acceptable intake per day of a leachable in pharmaceutical products per day (for a lifetime).

Point of Departure (PoD):

Starting point in the calculation of PDE of leachables; it can be derived from the human dose or appropriate animal study.

Qualification Threshold (QT):

Threshold above which a leachable should be qualified for potential non-mutagenic toxicity unless the leachable is identified as being Class 1.

Safety Concern Threshold (SCT):

Threshold at or below which a leachable would have a dose so low as to present negligible safety concerns from mutagenic and non-mutagenic toxic effects unless the leachable is identified as being a leachable of high concern.

Simulated Drug Product:

Matrix or solvent that mimics closely the leaching characteristics of the drug product formulation with respect to leaching propensity and solubility of leachables.

Substance (Compound, Chemical, Chemical Entity):

An association of different elements or chemical entities which have a definite chemical composition and distinct chemical properties.

System:

The sum of individual components (or assemblies) which together perform a specific function, such as manufacturing, delivery or storage/packaging.

Threshold of Toxicological Concern (TTC):

Threshold at or below which a leachable is not considered for safety assessment for mutagenic effects as described in ICH M7.

8. REFERENCES

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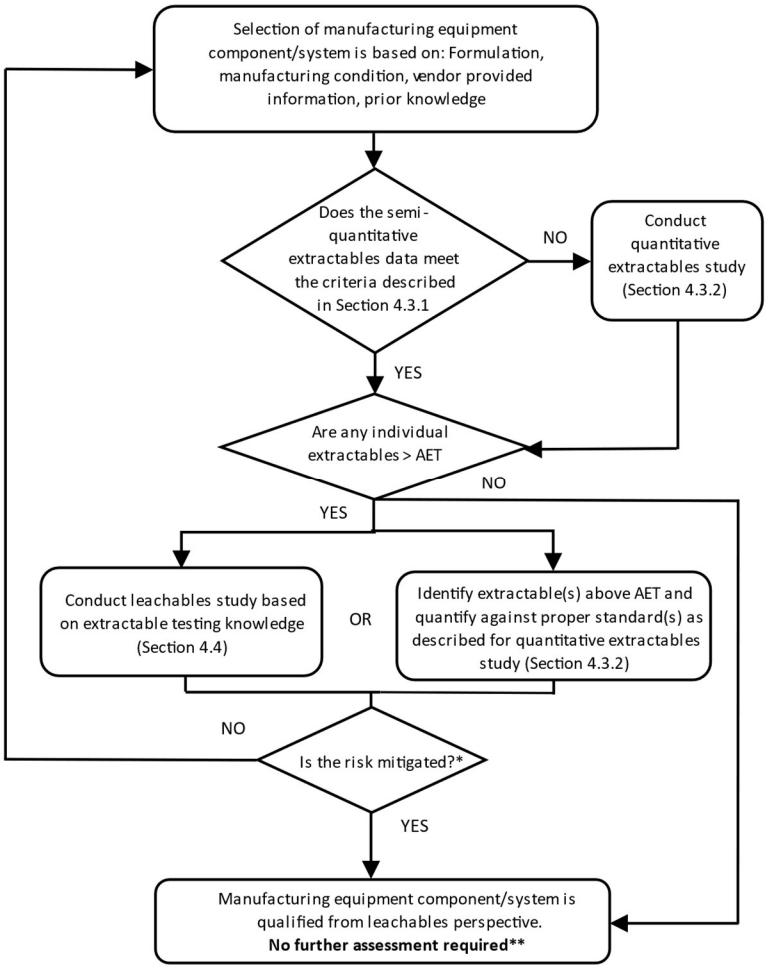
3. Ball D, Blanchard J, Jacobson-Kram D, McClellan RO, McGovern T, Norwood DL, et al. Development of Safety Qualification Thresholds and Their Use in Orally Inhaled and Nasal Drug Product Evaluation. Toxicol Sci. 2007 Jun;97(2):226-36.

Appendix 1: Typical workflows for E&L risk assessment and risk control

The following diagrams illustrate typical workflows for E&L overall risk assessment and risk control, for component qualifications for manufacturing components/systems packaging (Figure 4) and packaging and delivery device components/systems (Figure 5). Typically for manufacturing components/systems and under most circumstances for packing systems, a safety assessment of leachable studies considering worst case conditions is expected. However, under certain low risk circumstances, alternative approaches can be proposed. In all instances, similar to the examples given in Table A.1.1 and Table A.1.2 and where other low-risk scenarios could occur, the approach taken should be justified (see Table A.1.1 and Table A.1.2). Overall, it is expected that the extent of data requirements and subsequent quality and safety assessment is commensurate with the overall level of risk.

Figure 4: Typical workflow for E&L assessment related risk identification and mitigation for manufacturing components/systems



Refer to Section 4.3 for method qualification and chemical identification expectations as well as scenarios where a leachable study is recommended.

* Amount of extractable(s) or leachable(s) are below the applicable safety threshold for each compound.

** For manufacturing process employing multiple components constructed with the same or similar material, cumulative leachables risk should be assessed for the final drug product (see Section 3.4.1).

Figure 5: Typical workflow for E&L assessment related risk identification and mitigation for packaging and delivery device components

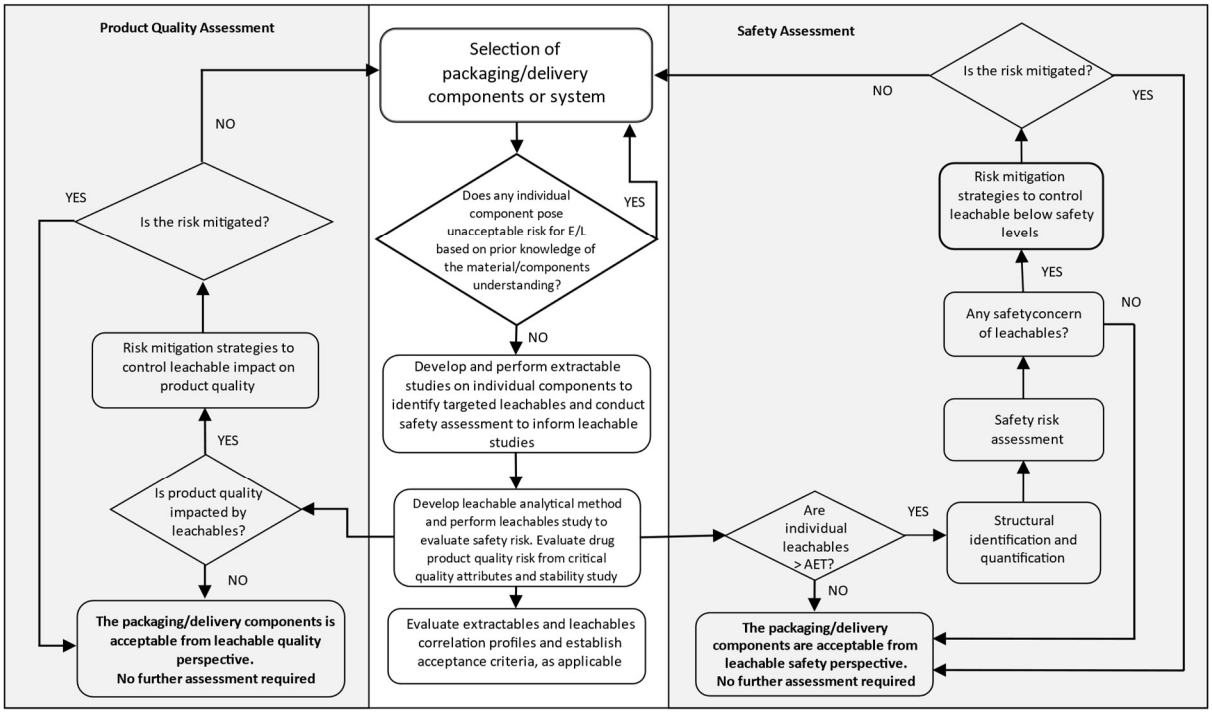


Table A.1.1: Manufacturing Equipment Components/Systems Scenarios

Risk Scenario	Potential Outcome
Scenario 1: Solid oral drug product manufactured using equipment components compliant with relevant regional food and/or pharmaceutical grade requirements (See Section 3.2).	Components considered qualified without additional extractables or leachables testing.
Scenario 2: Liquid oral drug product using polymeric manufacturing equipment/systems compliant with relevant regional food-contact safety regulations, use of these materials is consistent with the relevant regulations, and the leaching propensity of the drug product is not greater than identified in the relevant regulation (See Section 3.2).	Components may be considered qualified without additional extractables or leachables testing
Scenario 3: No manufacturing components/systems extractables above the applicable AET in a semi-quantitative extractable study (See Section 4.3.1).	

Scenario 4: All manufacturing equipment extractables detected, identified, and quantified in the quantitative extractable study above the applicable AET are below their applicable safety threshold (TTC/QT or compound-specific AI/PDE) (See Section 4.3.2).	Components may be considered qualified without additional extractables or leachables testing.

In general, comprehensive extractable and leachable data should be provided for all primary packaging components/systems and delivery device components. However, for overall low-risk scenarios (see Figure 2, Section 3.2) an abbreviated data package that includes a quantitative extractables study may be adequate with justification. See Section 3.4 for situations where a leachable study should be conducted to address the specific concerns and demonstrate acceptability of the components.

Table A.1.2: Examples For Abbreviated Data Package for Packaging and Delivery Device Components

Examples*	Potential Outcome
Example 1: Container closure system components for oral drug products are compliant with regional food contact regulations including composition, fabrication, specification, testing results, and in-use limitations specified therein (See Section 3.2).	Components may be considered qualified without additional extractables or leachables testing.
Example 2: Frozen, non-lyophilized drug product stored in a well-characterized packaging system (i.e., prior knowledge provided by the applicant). Drug product is thawed and administered within a short time-period and the duration between initiation of filling and freezing is also short (e.g., < 24 hours) (See Section 3.4.1).	Quantitative extraction studies using appropriate solvent with adequately exaggerated duration may be considered qualified.
Example 3: Delivery device components with very short/transient contact with oral drug products (e.g., oral syringes, oral dosing cups) are compliant with regional food contact regulations.	Components considered qualified without additional extractables or leachables testing.

Note 1 for Table A.1.1 and Table A.1.2:

Refer to section 4.3 for recommendations for extractable and leachable study, as appropriate.

Refer to section 3.5 for recommendation for appropriate documentation and compliance, as appropriate.

*If no or few extractables are detected above the AET, and below their applicable safety threshold (such as Class 3 leachables; See Section 6), in conjunction with prior knowledge an abbreviated data package may be warranted with adequate justification. When an abbreviated data package is proposed, communications with relevant regional Regulatory Agency/Health Authority is recommended to align on approach.

Appendix 2: Types of Studies

Table A.2.1: Summary of Extractable, Leachable and Simulated Leachable Studies

Study Type	Summary
Extractable	**Experimental Conditions:** Employs relatively aggressive conditions incorporating solvents and extraction conditions relevant to the anticipated leaching propensity of the drug product formulation under worst-case conditions to extract a greater number and/or amount of chemical entities than generated under actual-use conditions without inducing a chemical change in chemical entities or material being extracted. Commonly, a range of solvents that are representative of the drug product formulation are used. **Purpose:** Material/component characterization and to provide suitable data for hazard assessment to guide component selection. Under certain low risk scenarios (see Appendix 1), quality risk assessment of extractables may be leveraged for material/component qualification. Generate chemical entities (potential leachables) that exaggerate (in number and quantity) what will be observed as actual leachables. Evaluate chemical entities that may practically be expected to leach under intended use conditions. Identify potential leachables to enable hazard assessment and safety risk assessment as applicable.
Leachable	**Experimental Conditions:** Testing of the to-be-marketed drug product over shelf-life and in-use stability. Data may be supplemented with data from drug product using accelerated stability storage conditions if relevant. **Purpose:** Quantify and monitor target leachables over shelf-life and in-use. Identify and characterize unanticipated (non-target) leachables > AET. Enable toxicological risk assessment of observed leachables over shelf-life and in-use.
Simulated Leachable	**Experimental Conditions:**

	Testing of the manufacturing components and/or to-be-marketed drug product container closure system with a simulated drug product under conditions that simulate manufacturing and/or long-term storage conditions (pH, temperature, duration). Data may be supplemented using accelerated stability conditions if relevant. **Purpose:** Quantify and monitor target leachables over long-term storage and in-use. Identify and characterize unanticipated (non-target) leachables > AET. In rare circumstances when justified and concurred by regional regulatory authority, may be used in lieu of a leachable study for toxicological risk assessment.

Refer to Section 4.3 for detailed recommendations for extractable and leachable study, as appropriate.

Appendix 3 AET Calculations

Each of the examples provided are based upon using the applicable SCT (µg/day) for the drug product. In some instances, an alternative starting point may be pertinent (such as for a potential Class 1 leachable). In all calculations, worst-case assumptions such as maximum approved dosing of the drug product should be assumed. Common examples for both extractables and leachables studies are provided. Calculation of the AET should clearly indicate what the units are and how the calculation was performed. Regardless of the units used to express the AET, the final value for a given study should always equate to the same patient exposure level (i.e., the SCT multiplied by the analytical uncertainty factor [UF]).

Maximum Daily Dose (MDD) and Safety Concern Threshold (SCT)

For each product the calculation of the AET should be based on the MDD. The MDD is the maximum approved dose of a drug administered in a single day.

To determine the SCT, both the TTC and QT should be considered, as indicated in Table 1. The lowest of these values determines the SCT.

Intermittent Dosing

If a drug is not administered every day, for derivation of the applicable TTC ICH M7 is followed (e.g., when total number of dosing days is ≤30, the TTC = 120 µg).

For derivation of the QT, when total number of dosing days is ≤30 days or the dosing frequency is once per month or less, the ≤ 1 month QT can be used.

Multi-day Products

For products that are applied and may remain in place for multiple days (e.g. multi-day patches, depot injections, implants), the applicable TTC is defined by the total duration of treatment. For mutagenic impurities, per ICH M7 an average daily exposure should be used. For non-mutagenic leachable, the default assumption is that all leachables migrate within a day. In this case, the applicable QT is defined by the total number of applications. A slower migration rate would decrease the daily dose to a non-mutagenic leachable but increase the number of dosing days. A slower migration rate should be justified with data.

Example AET Calculations

Extractable Scenario 1: Filter used as part of a manufacturing process for a liquid drug product

(1) AET (µg/filter) = SCT (µg/day) × *UF* × Doses per drug product batch* ÷ Filters/batch

(2) AET (µg/g filter) = AET (µg/filter) ÷ Weight (g)/filter

(3) AET (µg/mL extraction solvent) = AET (µg/filter) ÷ Extraction solvent (mL)/filter

(4) AET (µg/cm^2) = AET (µg/filter) ÷ Contact surface area (cm^2)/filter

*The MDD administered in a single day and the minimum potential batch size should be used to determine the number of doses per drug product batch (i.e., the worst-case scenario). Thus, if the maximum approved dose given in a single day is 100 mg (= 0.1 g) and the minimum potential batch size in 1 kg (= 1000 g), the doses per drug product batch is 1000 g/batch ÷ 0.1 g/dose = 10,000 doses per drug product batch.

Extractable Scenario 2: Rubber vial stopper as part of CCS for a liquid drug product

(1) AET (µg/stopper) = SCT (µg/day) × *UF* × Volume/vial (mL/stopper) ÷ Maximum dose in a day (mL)*

(2) AET (µg/g stopper) = AET (µg/stopper) ÷ Stopper weight (g)

(3) AET (µg/mL extraction solvent) = AET (µg/stopper) ÷ Extraction solvent (mL)/Stopper

(4) AET (µg/mL extraction solvent) = AET (µg/g stopper) ÷ Extraction solvent (mL)/gram of Stopper

*The maximum approved volumetric dose administered in a single day should be used (i.e., the worst-case scenario). If dosing is described on a mass basis (e.g., mg/day), it should be converted to a volume (mL) based upon the concentration of the active ingredient. Thus, if the maximum approved dose given in a single day is 100 mg (= 0.1 g) and the concentration of the drug product is 10 mg/mL, the maximum

dose in a day for the calculation is 100 mg ÷ 10 mg/mL = 10 mL.

Leachable Scenario 1: Leachables for manufacturing equipment for liquid drug product

(1) AET (µg/batch) = SCT (µg/day) × *UF* × Doses per drug product batch*

(2) AET (µg/mL drug product) = SCT (µg/day) × *UF* ÷ Maximum dose in a day (mL)

*The MDD administered in a single day and the minimum potential batch size should be used to determine the number of doses per drug product batch (i.e., the worst-case scenario). Thus, if the maximum approved dose given in a single day is 5 mL and the minimum potential batch size in 10 L (= 10,000 mL), the doses per drug product batch is 10,000 mL/batch ÷ 5 mL/dose = 2,000 doses per drug product batch.

Leachable Scenario 2: Leachables for a prefilled syringe (PFS)

(1) AET (µg/mL drug product) = SCT (µg/day) × *UF* ÷ Maximum dose in a day (mL)*

(2) AET (µg/PFS) = AET (µg/mL drug product) × Volume per PFS (mL)

*The maximum approved volumetric dose administered in a single day should be used (i.e., the worst-case scenario). If dosing is described on a mass basis (e.g., mg/day), it should be converted to a volume (mL) based upon the concentration of the active ingredient. Thus, if the maximum approved dose given in a single day is 10 mg and the concentration of the drug product is 10 mg/mL, the maximum dose in a day for the calculation is 10 mg ÷ 10 mg/mL = 1 mL.

Appendix 4: Potency Classes for Leachables

The chemical nature of potential leachable compounds is varied as are their safety databases. In order to remain patient protective while maintaining a practical approach to setting safety thresholds, a leachables classification scheme has been developed, in addition to the thresholds applied in the guideline. The classification scheme is based on systemic effects and is broadly applicable to all routes of administration. However, the concentration thresholds applicable to drug products with specific routes of administration as indicated in Section 6.1 Table 1 are not impacted by this classification scheme. As such, the default concentration thresholds for potential local effects of a leachable are the same regardless of leachable class.

Class 1 leachables are generally those compounds for which the thresholds for mutagenic and systemic effects as described in this guideline have not been demonstrated to be sufficiently patient protective. Thus, for Class 1 leachables an acceptable exposure level should be

established on a compound-specific basis. Class 1 includes: ICH M7 cohort of concern compounds, ICH M7 Class 1 compounds with an AI < 1.5 µg/day, and non-mutagenic leachables with a derived Permitted Daily Exposure (PDE) following the methodology described in Appendix 5 for which the established QT values may not be protective of patient safety (see Appendix 6).

Class 2 is the default leachable classification and includes compounds for which the chronic parenteral administration thresholds for mutagenicity (TTC) and systemic toxicity (QT), as described in this guideline, are considered to be sufficiently patient protective. This includes all compounds for which a PDE was not specifically listed in this guideline.

Class 3 leachables are compounds established to have relatively low potency for systemic toxicity with derived chronic parenteral PDE in excess of the levels at which leachables are typically observed. Class 3 leachables would not require further safety qualification if observed at daily exposure levels < 1.0 mg/day.

A summary of these leachables classes is provided in Table A.4.1, below. Leachable levels greater than identified in Table A.4.1 should be scientifically justified as described in Appendix 5.

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952 **Table A.4.1: Potency Classes for Leachables**

Class 1 – Leachables to be avoided Mutagens/Predicted Mutagens Leachables that are part of the ICH M7 cohort of concern (aflatoxin-like-, N-nitroso-, and alkyl-azoxy compounds). Leachables meeting criteria for ICH M7 Class 1 impurities and an AI < 1.5 µg/day. Non-mutagens/Predicted Non-Mutagens Leachables that have a derived parenteral PDE for which the established QT values may not be protective of patient safety (see list below). *ICH Q3E Class 1 leachables should be avoided when practically feasible and exposure should not exceed a scientifically justified compound-specific acceptable exposure level.*
Class 2 – Leachables to be limited Mutagens/Predicted Mutagens Leachables meeting criteria for ICH M7 Class 1 impurities and an AI ≥ 1.5 µg/day. Leachables meeting criteria for ICH M7 Class 2 or 3 impurities. *ICH Q3E Class 2 mutagenic (or predicted mutagenic) leachables should not exceed (1) the TTC or less-than-lifetime TTC as appropriate or (2) the QT pertinent to the drug product.* Non-mutagens/Predicted Non-Mutagens Leachables considered to have a parenteral PDE > QT (excluding those established as Class 3) following the methodology described in Appendix 5. *ICH Q3E Class 2 non-mutagenic (or predicted non-mutagenic) leachables are considered qualified up to the QT pertinent to the drug product without further safety justification.*
Class 3 – Leachables with relatively low toxic potential Non-mutagenic leachables established to have a chronic parenteral PDE in excess of the levels at which leachables are typically observed. *ICH Q3E Class 3 leachables are considered qualified up to 1.0 mg/day or the compound specific PDE (see Table below and Supporting Document) without further safety justification.*

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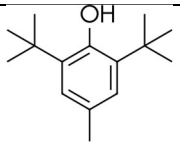
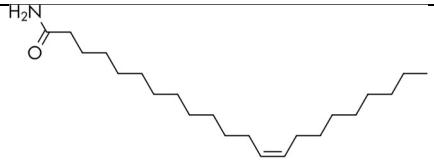
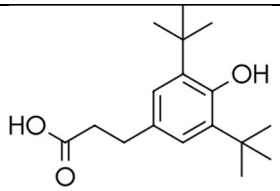
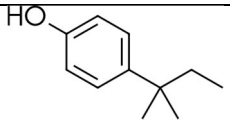
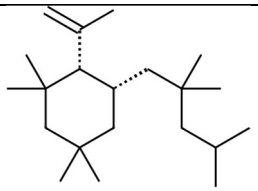
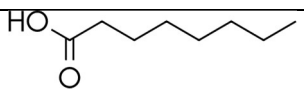
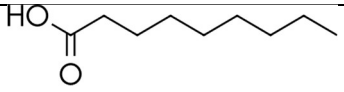
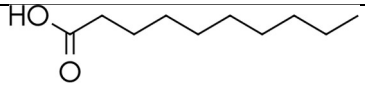
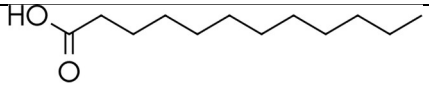
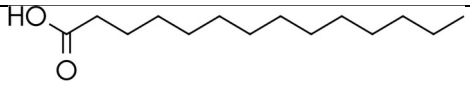
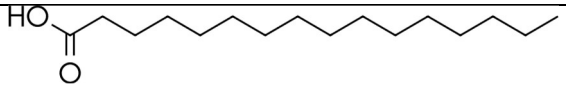
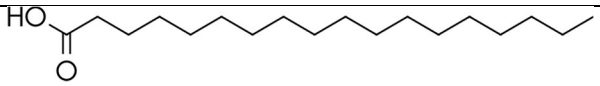
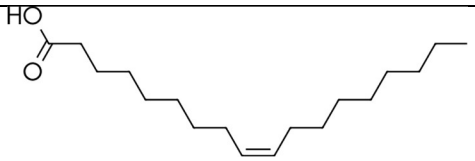
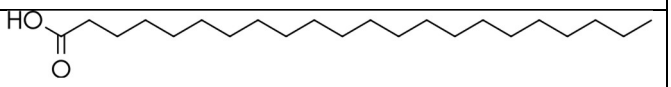
Class 1 Leachables to be avoided

Compound	CAS#	Acute Acceptable Exposure Level (µg/day)		Chronic PDE (µg/day)		Associated Material
		Oral	Parenteral	Oral	Parenteral	
Benzo(a)pyrene	50-32-8	13	1.3	2.6	0.26	Carbon black
Bisphenol A	80-05-7	2,083	21	417	4	Polycarbonate and epoxy resin

Class 3 Leachables With Relatively Low Toxic Potential (Chronic Parenteral PDE ≥ 1 mg/day). Monographs In Supporting Documents.

Compound	CAS#	Chemical Structure
2,6-Di-tert-butyl-4-methylphenol (BHT)	128-37-0	
Erucamide	112-84-5	
3-(3,5-Di-tert-butyl-4-hydroxyphenyl) propanoic acid	20170-32-5	
4-Tert Amylphenol	80-46-6	
Rubber oligomer $C_{21}H_{40}$	114123-73-8	
Fatty Acids		
Caprylic acid (C8)	124-07-5	
Nonanoic acid (C9)	112-05-0	

Capric acid (C10)	334-48-5	
Lauric acid (C12)	57-10-3	
Myristic acid (C14)	544-63-8	
Palmitic acid (C16)	57-10-3	
Stearic acid (C18)	57-11-4	
Oleic acid (C18)	112-80-1	
Docosanoic acid (C22)	112-85-6	

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Appendix 5: Methods for Establishing Exposure Limits

Background

For Class 1 leachables and Class 2/3 leachables exceeding their applicable safety threshold as defined in this guideline, further safety assessment is performed to establish the potential risk associated with exposure to these leachables when a patient is administered a specific drug product. Permitted Daily Exposure (PDE) values intended to support safe exposure to a compound in any drug product are not currently established for the vast majority of potential leachables. Furthermore, due to the varied nature of currently available drug products and the complexity of extractables and leachables safety risk assessment, a one size fits all approach, such as an established PDE, is not always most pertinent. Although the focus of this guideline is not on the generation of acceptable exposure levels for individual compounds, the need for compound-specific limits on a product-by-product basis may commonly arise. Therefore, this appendix provides guidance to appropriately establishing the safety of leachables for a variety of drug product types and administration scenarios using a risk-based approach.

The extent of the information considered sufficient to conclude on the acceptability of potential patient exposure levels for a leachable may vary extensively and there are multiple methodologies which may be employed to establish this acceptability. The most straight-forward methodology is to employ already established safe exposure levels which have conservatively assumed worst scenarios. Thus, when there is an established PDE in an available ICH guidance (e.g., Q3C or M7) it is sufficient to refer to this value assuming all requisite considerations are met. Alternatively, an acceptable exposure derived using similar methodologies and scientific principles as previously established in such guidelines may be deemed more applicable or necessary. In still other scenarios, the dose ratio between a well-defined, supported and justified NOAEL and the anticipated patient exposure may be so large (e.g., >10,000) that a detailed derivation may not be necessary.

Though in certain circumstances, *in vitro* and/or *in vivo* studies (as a last resort) may be deemed necessary to establish an acceptable exposure level, scientific justification (if applicable) via available *in silico* analyses and through read across to similar compounds (i.e., surrogate compound[s]) is encouraged to establish acceptable exposure levels.

Although a variety of *in silico* toxicological tools are available, mutagenicity is the only

toxicological endpoint for which such an appropriately conducted evaluation is currently well-established for stand-alone use in lieu of biological data within the context of this guideline (see ICH M7). However, with appropriate scientific justification, predictions of other toxicological endpoints using *in silico*, *in vitro*, or *in vivo* models should be incorporated into the safety risk assessment to supplement any existing data in a weight-of-evidence risk-based approach. Within each of these categories, greater priority should be given to data from validated models that account for the relevant exposure route(s).

Due to the limited nature or even lack of toxicological datasets for a large number of potential leachables, a read-across approach may also be incorporated. In a read-across approach, toxicological data for a surrogate compound (or multiple surrogates) with pertinent toxicological data are used to support the safety assessment of a leachable of interest either as part of a weight-of-evidence approach or in lieu of data for the leachable of interest when none is available. Safety assessments incorporating a surrogate compound should provide clear justification for the selection of the surrogate(s). There are various attributes that should be considered (if known) during the selection of a suitable surrogate, including mode of action, the principal toxicophore and surrounding chemical environment (e.g., presence of functional groups that may impact biological activity), overall structural similarity, toxicokinetic properties, physicochemical properties (e.g., polarity, solubility, ionizability, and molecular weight). When properly justified, *in silico* tools and data from NAMs may be used to support the selection of surrogates and inform the read-across approach, but the above-mentioned criteria need to be considered. How a surrogate is incorporated into the safety assessment for the leachable of interest should be scientifically justified. Potential uncertainties related to the read-across approach should also be indicated and appropriately accounted for, such as when using for an acceptable exposure level determination (see F7 discussion below).

Data to be Evaluated and Incorporated into the Safety Assessment

In order to establish the safety of a leachable in a specific drug product, a thorough safety assessment of the compound should be provided. Data elements to be included (where data are available) are listed below. The relevance and quality of these datasets should also be assessed. As noted above, any use of surrogate compound data with *in silico* analyses should also be incorporated into the safety assessment and justified. Additionally, if several observed leachables are grouped together for evaluation, the details and justification of this grouping should be included.

Pharmacological/Biological Data

- Consider available *in vivo* or *in vitro* data that suggest the potential for biological effects that could impact the overall safety assessment (e.g., endocrine disruption, anticholinergic activity).

Toxicokinetics (TK)

- Assess and summarize data relevant to the drug product's route of administration
- Consider potential differences between absorption and bioavailability, especially when route-to-route extrapolations are required.
- Bioaccumulation potential should be considered.

Systemic Toxicity

- Summarize relevant acute, subacute/subchronic and chronic toxicity studies.
- Indicate relevance of data to humans.
- Identify critical study (or studies) for evaluating human systemic toxicity potential.

Sensitization Potential/Local Irritation

- Relevant available clinical and non-clinical data (supplemented with *in silico* evaluation, if justified) should be summarized.
- Regulatory classifications (or lack thereof) may be leveraged as pertinent.

Developmental and Reproductive Toxicity (DART)

- In addition to summarizing available DART studies, data and/or classifications with respect to endocrine disrupting properties should evaluated and included.

Genotoxicity and Carcinogenicity

- Summarize available data and indicate potential relevance to humans.
- If data are not available, *in silico* methods consistent with ICH M7 should be used for evaluation (Note: ICH M7 Class 4 is not applicable to leachables).
- Mechanism(s) for genotoxicity and/or carcinogenicity should be provided if applicable as this is particularly pertinent for acceptable exposure determinations.

Additional Information

- Additional pertinent information to the safety assessment should also be included as available.
- Examples: Existing heath-based risk limit/assessments, clinical and epidemiological data, toxicological data from similar/related compounds

Acceptable Exposure Calculations

The PDE concept has been implemented as a health-based exposure limit in ICH guidelines in addition to other health-based limits such as the Acceptable Intake (AI). The process for calculation of a PDE is generally aligned across these guidelines. This same basic approach has been used to generate PDE values in support of the identified qualification thresholds of the current guideline (with the inclusion of additional modifying factors for bioavailability and for when a read-across approach is used). This approach is briefly described and summarized below and may be used as the basis for an acceptable exposure level for a leachable in a specific drug product.

Although the method for deriving an acceptable exposure level described here is based on the PDE methodology described in other ICH guidelines, it should be noted that the acceptable exposure may not necessarily be the same as the PDE. Whereas the PDE is by definition an exposure level for lifetime and is applicable across many products, the product-specific acceptable exposure takes into account the duration of exposure and maximum daily dose. Subsequent to review and evaluation of the available data and information for the leachable as described above, the derivation process begins with the selection of an appropriate point of departure (PoD) and then applying modifying factors (F1–F7). The most relevant study should be used to select the PoD, taking into consideration the species used, the route and duration of exposure, the toxicological endpoints monitored, and the quality of the study data, if justified, it may not always be necessary to select the lowest NO(A)EL as a PoD. Previous guidelines have used specific modifying factors for inter- and intraspecies variability (F1 and F2, respectively), duration of the study from which the PoD is taken (F3), severity of the toxicity (F4), and a factor to account for the absence of a NOAEL (F5). As leachables cover a wide chemical space, bioavailability via various administration routes may vary. Since toxicity data are often only available for a single route, the incorporation of an additional modifying factor (F6) is recommended in the current guideline to account for differences in bioavailability when route-to-route extrapolation is required. Additionally, as noted previously, a PoD from a surrogate compound (read across approach) may also sometimes be necessary. Thus, another modifying factor (F7) to account for uncertainty related to using this surrogate compound is recommended.

As the criteria for selecting values for F1–F5 have been detailed in existing guidelines, they are not repeated here. However, the newly introduced modifying factors (F6 and F7) pertinent to leachables are summarized below.

F6 = A variable factor to account for route of exposure extrapolation (e.g., oral to parenteral).

In the absence of sufficient toxicity data on the leachable via the intended route of exposure of the drug product, F6 should be used to adjust for any pertinent difference in bioavailability between the PoD study route of administration and the drug product route of exposure. Ideally, F6 should be based on bioavailability of the parent compound. If a radiolabel study is used, it should be referred to as absorption because it is not clear if the radiolabel is the parent, a metabolite, or a combination of parent and metabolites. If the quality of data is good, the relative bioavailability estimate can be used to directly inform F6. When there is significant uncertainty for the bioavailability estimate, default factors may alternatively be applied. For example, when using oral toxicity data to derive a parenteral acceptable exposure level:

F6= 100 when oral bioavailability is <1% (divide by a modifying factor of 100)

F6= 10 when oral bioavailability is ≥ 1% and <50% (divide by a modifying factor of 10)

F6= 2 when oral bioavailability is ≥50% and <90% (divide by a modifying factor of 2), and

F6=1 when oral bioavailability is ≥ 90% (divide by a modifying factor of 1)

In the absence of sufficient in vivo data, additional approaches should be employed as part of a weight-of-evidence strategy or in lieu of in vivo data. For example, a NAM approach (combining *in vitro* data estimating absorption and internal clearance, with an *in silico* PBPK model) can be used to generate data to assess bioavailability if properly supported and scientifically justified. Alternatively, a default modifying factor of 100 is suggested for F6, with smaller values requiring justification (e.g., reasoning based on the physicochemical characteristics of the compound). When suitable bioavailability data are available for a surrogate molecule allowing a read-across approach these data may be leveraged to inform the bioavailability estimate, if sufficiently justified.

For some routes, such as inhalation, additional considerations are warranted when determining an appropriate F6 value. For example, for an inhalation toxicology study, data on respiratory tract deposition, respiratory absorption rate and pulmonary metabolism may inform on F6.

For dermal routes, if toxicokinetic data are available these can be used to estimate the systemic dose. The parenteral QT can be referred to when evaluating the estimated total daily systemic dose of the leachable. In the absence of toxicokinetic data, when extrapolating from dermal dose to systemic dose, a default absorption of 70% or 50% is assumed to be sufficiently conservative for most organic solvent-based dilutes and water-based or dispersed dilutes,

respectively. If both the molecular weight is greater than 500 and the logPow is either below –1 or above 4, a default absorption factor of 10% is assumed. Leachables may penetrate the skin to a greater extent when present in dermal drug products that are formulated for enhanced percutaneous absorption or where skin integrity may be compromised. A higher rate of absorption should be assumed in such cases.

F7= A variable factor that may be applied if a Read Across Approach is used.

When read across strategy is utilized, a factor of up to 5 may be used depending on the level of (dis)similarity to the leachable compound of interest. In general, when a surrogate is considered similar based on the criteria described in this guideline, an F7 of 1 may be applicable.

References

Copies of articles (or other documents) referenced to support a proposed PDE should be provided.

Margin of Safety (MOS) and justification for leachable levels higher than a calculated acceptable exposure level or established PDE

For each substance for which an acceptable exposure level (e.g., PDE or AI) has been determined, a margin of safety can be calculated using the following formula:

$$\text{Margin of Safety} = \frac{\text{Acceptable exposure level}}{\text{Potential patient exposure}}$$

For any substances with an MOS <1, risk mitigation measures (such as the selection of alternate materials) that might reduce or eliminate the leachable of concern should be considered. Alternatively, it should be demonstrated that a limit greater than the acceptable exposure level (e.g., PDE) does not pose a safety concern for a specific drug product. An acceptable exposure level to a leachable higher than the calculated or established PDE may be acceptable in certain cases, taking into account relevant product-specific considerations. These cases could include, but are not limited to, the following situations:

- Intermittent administration of the drug to patients;
- Short term administration (i.e., 30 days or less);
- Limited patient population (e.g., adult males only);
- Specific indications (e.g., life-threatening, unmet medical needs, rare diseases).

Additionally, it should be noted, that for drugs administered for less than lifetime to the patient,

it may be appropriate to use a lower value for F3 than would usually be applied where a toxicity study of short-term exposure is selected as PoD. In this case an acceptable exposure level is derived, as opposed to PDE. If additional animal studies are available with longer duration, these may have NOAEL values based on findings that may not be relevant to shorter term exposures and therefore may not be the most appropriate PoD for a given drug product. However, while toxicity studies of short-term exposure may be acceptable as a PoD in this circumstance, this does not include LD_{50} studies.

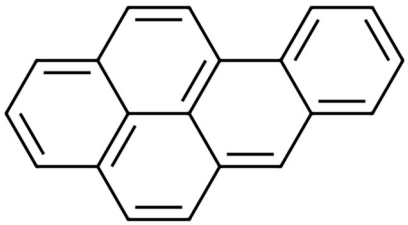
In cases where a product is administered intermittently, a subfactor approach for F2 as described in ICH Q3D can be applied if supported by data. Alternatively, the value for F3 can be modified.

Table A.5.1: Example considerations for a weight of evidence justification when qualification of leachables is necessary. Non-animal methods should be prioritized where possible.

Toxicological Endpoint	**Non-Animal Methods (with justification)**	***In vivo* Models**
General Systemic Toxicity	Read across	Qualification study(ies) as described in ICH Q3A and Q3B Regional guidance (such as USP)
Local Toxicity	Read across *In vitro* models: Cytotoxicity (USP <87>, <1031>) Bovine corneal opacity (BCOP: OECD 437)	Toxicological qualification study(ies) as described in ICH Q3A and Q3B should be considered Local Tolerance as assessed according to other standards (such as ISO 10993)
Genotoxicity	*In silico* models as per ICH M7	Refer to ICH M7

Appendix 6: Monographs for Class 1 Leachables

Benzo[a]pyrene



Summary of Acute Acceptable Exposure Level and Chronic PDE Values for Benzo[a]pyrene (CAS# 50-32-8)

Benzo[a]pyrene		
Administration Route	**Oral (µg/day)**	**Parenteral (µg/day)**
Acute Acceptable Exposure Level*	13	1.3
Chronic PDE	2.6	0.26

*Acute acceptable exposure level is applicable to ≤1-month daily administration

Introduction

Benzo[a]pyrene (BaP) is a polycyclic aromatic hydrocarbon (PAH) consisting of five fused benzene rings. It is not produced or used commercially but is formed as a result of incomplete combustion of organic matter. BaP may leach from materials in which carbon black is present.

BaP is a mutagenic carcinogen and as such, control according to the current version of ICH M7 is appropriate, in addition to the relevant Acceptable Exposure or PDE values derived below. Based on a non-mutagenic endpoint, two oral and two parenteral values for BaP were developed for ICH Q3E.

Safety Summary and Limiting Non-Mutagenic Toxicity

Oral exposure to BaP has been shown to result in developmental toxicity (including developmental neurotoxicity), reproductive toxicity, and immunotoxicity in repeat dose toxicity studies, including adult and juvenile animals. Overall, human studies report toxicological effects that are generally analogous to those observed in animals, and provide qualitative, supportive evidence for hazards associated with BaP exposure.

Based on critical non-mutagenic effects of BaP, the non-GLP oral developmental toxicity study

in neonatal rat (Chen et al., 2012) was selected as the PoD study for oral and parenteral PDE derivation.

Oral Acceptable Exposure and PDE

The rat neurodevelopmental study by Chen et al., 2012 administered doses of BaP at 0, 0.02 mg/kg, 0.2 mg/kg, and 2 mg/kg on postnatal day 5 to 11 by oral gavage. Altered responses in three behavioral tests (Morris water maze, elevated plus maze, and open field tests) were selected to represent the critical effect of abnormal behavior, due to the consistency of the observations across groups/studies (i.e., each of these responses were affected in two separate cohorts of rats, including testing as juveniles and as adults; similar effects in these behavioral tests were observed across studies) and sensitivity of these responses, and the observed dose-response relationship of effects across dose groups. Benchmark dose (BMD) modeling for each of the three endpoints resulted in BMD lower bound for 1 standard deviation (BMDL1SD) values in the range 0.092−0.16 mg/kg-day. Taking the lower end of the range, 0.092 mg/kg-day, was selected to represent the PoD from the neurodevelopmental study.

Oral Calculation	
PoD	**0.092 mg/kg/day**
BW	**50 kg**
F1 (juvenile rat)	**7**
F2 (intra-species variability)	**10**
F3 (PoD study duration: postnatal day 5 to 11)	**1 for Acute Acceptable Exposure Level**
	5 for Chronic PDE critical period of brain development not covered by PoD study.
F4 (Behavioural effects)	**5**
F5 (BMDL1SD)	**1**
F6 (PoD route extrapolation)	**Not applicable**
Acute Acceptable Exposure Level = 0.092 mg/kg/day x 50 kg / (7 x 10 x 1 x 5 x 1) = 0.013 mg x 1,000 µg/mg = 13 µg/day	
Chronic PDE = 0.092 mg/kg/day x 50 kg / (7 x 10 x 5 x 5 x 1) = 0.0026 mg x 1,000 µg/mg = 2.6 µg/day	

Parenteral Acceptable Exposure and PDE

In the absence of parenteral administration repeat dose toxicity studies, the same POD study was used to derive the parenteral PDE with the inclusion of a bioavailability modifying factor (F6), based on physiochemical characteristics of BaP (MW = 252.3 g/mol and predicted LogP 3.0 (PubChem, 2024)).

Parenteral Calculation	
PoD	**0.092 mg/kg/day**
BW	**50 kg**
F1 (juvenile rat)	**7**
F2 (intra-species variability)	**10**
F3 (PoD study duration: postnatal day 5 to 11)	**1 for Acute Acceptable Exposure**
	5 for Chronic PDE critical period of brain development not covered by PoD study.
F4 (Behavioural fetal effects)	**5**
F5 (BMDL)	**1**
F6 (Physicochemical characteristics)	**10**
Acute Acceptable Exposure Level = 0.092 mg/kg/day x 50 kg / (7 x 10 x 1 x 5 x 1 x 10) = 0.0013 mg x 1,000 µg/mg = 1.3 µg/day	
Chronic PDE = 0.092 mg/kg/day x 50 kg / (7 x 10 x 5 x 5 x 1 x 10) = 0.00026 mg x 1,000 µg/mg = 0.26 µg/day	

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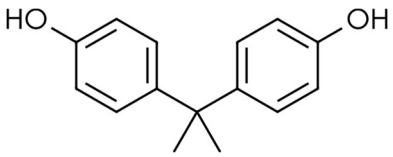
Bisphenol A



Summary of Acute Acceptable Exposures and Chronic PDE Values for Bisphenol A (CAS# 80-05-7)

Bisphenol A		
Administration Route	**Oral (µg/day)**	**Parenteral (µg/day)**
Acute Acceptable Exposure*	**2,100**	**21**
Chronic PDE	**420**	**4.2**

*Acute Acceptable Exposure value is applicable to ≤1-month daily administration

Introduction

Bisphenol A (BPA) is 4,4'-methanediyldiphenol where the methylene hydrogens are replaced by two methyl groups. It is a key building block of polycarbonate plastic and a precursor for the manufacturing of monomers of epoxy resins. BPA may be present in primary packaging material and manufacturing equipment used in the manufacturing process of medicines, in medicine containers, medicine/device combinations, and in parenteral nutrition bags (Parris et al, 2020).

Safety Summary and Limiting Toxicity

BPA is not mutagenic and non-genotoxic. ECHA listed BPA capable of producing skin sensitization responses in humans and may damage fertility or the unborn child. BPA is not a skin irritant; however, it is irritating to the eye (ECHA, 2024). The European Medicines Agency (EMA) obligates the use of an apical endpoint to minimize uncertainty in relation to human health risk assessment; ICH Q3E is aligned with EMA, and therefore non-mutagenic PDEs were derived for evaluation of BPA as a potential leachable in pharmaceutical products (EFSA EMA, 2023).

Oral Acceptable Exposure and PDE

BPA was tested in a two-generation study in mice (Tyl et al 2008). The GLP and OECD 416-compliant study in mice, evaluated dietary BPA concentrations of 0, 0.018, 0.18, 1.8, 30, 300,

or 3500 ppm (approximately 0.003, 0.03, 0.3, 5, 50, or 600 mg/kg/day) ad libitum. Concurrent positive control group of dietary 17β-estradiol (0.5 ppm; 28 per sex) was included to evaluate potential for endocrine disruption.

F0 generation animals received respective formulations in the diet for 8 weeks prior to mating (i.e., until ~14 weeks of age). The animals were then mated for a period of 14 days. Animals continued dosing through gestation (~20 days) and lactation (3 weeks).

No BPA-related effects at any dose were observed for adult mating, fertility or gestational indices, ovarian primordial follicle counts, estrous cyclicity, pre-coital interval, offspring sex ratios or post-natal survival, sperm parameters or reproductive organ weights or histopathology (including the testes and prostate). Systemic effects observed in adults were centrilobular hepatocyte hypertrophy at ≥300 ppm, reduced body weight, increased kidney and liver weights, centrilobular hepatocyte hypertrophy, and renal nephropathy in males. In conclusion, the NOAEL for reproductive toxicity was 300 ppm (~50 mg/kg/day) and NOEL for adult (F0) systemic toxicity was 30 ppm (~5 mg/kg/day).

Oral Calculations	
PoD	**5 mg/kg/day**
BW	**50 kg**
F1 (mouse)	**12**
F2 (intra-species variability)	**10**
F3 (POD study duration: 4 months)	**1 for Acute Acceptable Exposure**
	5 for Chronic PDE
F4 (No severe toxicity)	**1**
F5 (NOEL)	**1**
F6 (PoD route extrapolation)	**Not applicable**
Acute Acceptable Exposure = 5 mg/kg/day x 50 kg / (12 x 10 x 1 x 1 x 1) = 2.1 mg x 1,000 µg/mg = 2,100 µg/day	
Chronic PDE = 5 mg/kg/day x 50 kg / (12 x 10 x 5 x 1 x 1) = 0.42 mg x 1,000 µg/mg = 420 µg/day	

Parenteral Acceptable Exposure and PDE

In the absence of parenteral administration repeat dose toxicity studies, the same POD study was used to derive the parenteral PDE with the inclusion of a bioavailability modifying factor (F6). Oral systemic bioavailability of unconjugated BPA of 2.8% in rats and less than 1% in mice, monkey and dogs was reported (ANSES, 2013).

Parenteral Calculation	
POD	**5 mg/kg/day**
BW	**50 kg**
F1 (mouse)	**12**
F2 (intra-species variability)	**10**
F3 (POD study duration: 4 months)	**1 for Acute Acceptable Exposure**
	5 for Chronic PDE
F4 (No severe effects)	**1**
F5 (NOEL)	**1**
F6 (Mouse oral bioavailability < 1%)	**100**
Acute Acceptable Exposure = 5 mg/kg/day x 50 kg / (12 x 10 x 1 x 1 x 1 x 100) = 0.021 mg x 1,000 µg/mg = 21 µg/day	
Chronic PDE = 5 mg/kg/day x 50 kg / (12 x 10 x 5 x 1 x 1 x 100) = 0.0042 mg x 1,000 µg/mg = 4.2 µg/day	

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INTERNATIONAL COUNCIL FOR HARMONISATION OF
TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR
HUMAN USE (ICH)

ICH HARMONISED
GUIDELINE

ICH Q3E: GUIDELINE FOR EXTRACTABLES AND LEACHABLES

SUPPORTING DOCUMENTATION: CLASS 3 LEACHABLE MONOGRAPHS

Draft version

Endorsed on 01 August 2025

Currently under public consultation

At Step 2 of the ICH Process, a consensus draft text or guideline, agreed by the appropriate ICH Expert Working Group, is transmitted by the ICH Assembly to the regulatory authorities of the ICH regions for internal and external consultation, according to national or regional procedures.

ICH Q3E: GUIDELINE FOR EXTRACTABLES AND LEACHABLES

SUPPORTING DOCUMENTATION: CLASS 3 LEACHABLE MONOGRAPHS

Document History

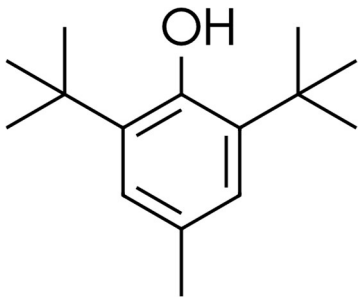
Code	History	Date
Q3E	Endorsement by the Members of the ICH Assembly under *Step 2a/b* and release for public consultation.	01/August/2025
Q3E Supporting Documentation	Endorsement by the Members of the ICH Assembly under *Step 2* and release for public consultation alongside the *Step 2a/b* ICH Q3E: Guideline for Extractables and Leachables.	01/August/2025

ICH Q3E: GUIDELINE FOR EXTRACTABLES AND LEACHABLES

SUPPORTING DOCUMENTATION: CLASS 3 LEACHABLE MONOGRAPHS

Table of Contents

2,6-Di-tert-butyl-4-methylphenol (BHT)



Summary Acute Acceptable Exposure Levels and Chronic PDEs for BHT (CAS# 128-37-0)

BHT		
Administration Route	**Oral (µg/day)**	**Parenteral (µg/day)**
Acute*	**25,000**	**12,500**
Chronic	**25,000**	**12,500**

*Acute Acceptable Exposure Level is applicable to ≤1-month daily administration

Introduction

2,6-Di-tert-butyl-4-methylphenol is commonly called butylated hydroxytoluene (BHT) is a synthetic antioxidant and/or stabilizer added to polymers used in the food, cosmetic, pharmaceutical, and petroleum industries (OECD, 2002; WHO, 1986). BHT is observed as a leachable or extractable associated with pharmaceutical manufacturing and packaging components/systems (Parris et al, 2020).

Safety Summary

Toxicity	Yes	No
Mutagenicity		X
Extreme or strong potency skin sensitizer		X
Skin and eye irritation	X (Slight)	
Systemic toxicity	X (Liver and adrenal)	

The Joint FAO/WHO Expert Committee on Food Additives (JECFA, 1996) established an acceptable daily intake (ADI) of 0-0.3 mg/kg/day; consistent with EFSA ADI of 0.25 mg/kg/day (EFSA, 2012).

Limiting Toxicity

Basis for Acceptable Exposure and PDE	
PoD Study:	GLP-compliant dietary 2-generation and carcinogenicity study (same study selected by EFSA to derive ADI value)
Species:	Rat
Doses:	25, 100, and 500 mg/kg/day (F0 generation) until end of lactation period. Groups of F1 generation received same doses until the 141–144 weeks, except high dose was 250 mg/kg/day
Observations and Limiting Toxicity:	Liver (relative weight increases, statistically significant increases liver enzymes and total cytochrome P450 content, histopathological correlates) and adrenal histopathological findings observed at ≥100 mg/kg/day
PoD:	NOAEL = 25 mg/kg/day
Reference:	McFarlane et al, 1997

Oral Acceptable Exposure Level and PDE:

Oral Calculations	
PoD	25 mg/kg/day
BW	50 kg
F1 (rat)	5
F2 (intra-species variability)	10
F3 (PoD study duration: 22 months)	1 for Acute Acceptable Exposure Level
	1 for Chronic PDE
F4 (Liver findings)	1
F5 (NOAEL)	1
F6 (PoD route extrapolation)	Not applicable
F7 (read across)	Not applicable
Acute Acceptable Exposure Level = 25 mg/kg/day x 50 kg / (5 x 10 x 1 x 1 x 1) = 25 mg x 1,000 µg/mg **= 25,000 µg/day**	
Chronic PDE = 25 mg/kg/day x 50 kg / (5 x 10 x 1 x 1 x 1) = 25 mg x 1,000 µg/mg **= 25,000 µg/day**	

Parenteral Acceptable Exposure Level and PDE:

In the absence of parenteral administration repeat dose toxicity studies, the oral PoD study was used to derive the parenteral values with the inclusion of a bioavailability modifying factor (F6). Liver and adrenal findings provide evidence that BHT is systemically bioavailable following repeated dietary administration. In addition, in silico predictions of absorption and oral bioavailability, respectively are as follows:

- Humans 98.4% and 51.8%
- Rats 95.3% and 49.1%

Based on weight of evidence, an F6 of 2 is applied.

Parenteral Calculations	
PoD	25 mg/kg/day
BW	50 kg
F1 (rat)	5
F2 (intra-species variability)	10
F3 (PoD study duration: 22 months)	1 for Acute Acceptable Exposure Level
	1 for Chronic PDE
F4 (Liver findings)	1
F5 (NOAEL)	1
F6 (Systemic toxicity and bioavailability: predicted)	2
F7 (read across)	Not applicable
Acute Acceptable Exposure Level = 25 mg/kg/day x 50 kg / (5 x 10 x 1 x 1 x 1 x 2) = 12.5 mg x 1,000 µg/mg = **12,500 µg/day**	
Chronic PDE = 25 mg/kg/day x 50 kg / (5 x 10 x 1 x 1 x 1 x 2) = 12.5 mg x 1,000 µg/mg = **12,500 µg/day**	

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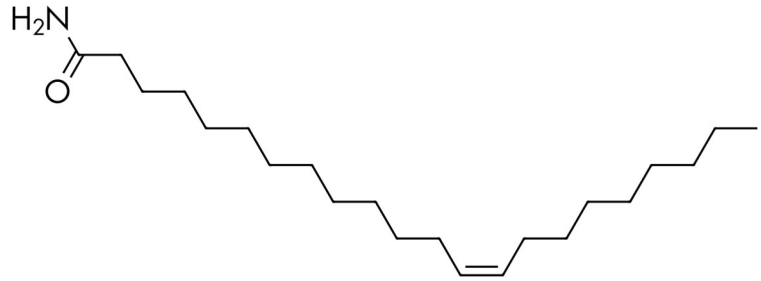
Erucamide



Summary Acute Acceptable Exposure Levels and Chronic PDEs for Erucamide (CAS#112-84-5)

Erucamide		
Administration Route	**Oral (µg/day)**	**Parenteral (µg/day)**
Acute*	**1,000,000**	**100,000**
Chronic	**200,000**	**20,000**

*Acute Acceptable Exposure Level is applicable to ≤1-month daily administration

Introduction

Erucamide is a primary fatty amide resulting from the condensation of the erucic acid carboxyl group with ammonia and is commonly used as a slip additive in the plastic manufacturing industry (Health Canada, 2019). Erucamide is observed as a potential leachable associated with pharmaceutical manufacturing and packaging components/systems.

Safety Summary

Toxicity	Yes	No
Mutagenicity		X
Extreme or strong potency skin sensitizer		X
Skin and eye irritation		X
Systemic toxicity	X	

Limiting Toxicity

Basis for Acceptable Exposure and PDE	
PoD Study:	OECD 408 and GLP-compliant 90-day oral gavage toxicity study
Species:	Rat
Doses:	100, 300 and 1,000 mg/kg/day (nominal dose)
Observations and Limiting Toxicity:	No adverse treatment-related effects were observed at any dose
PoD:	NOAEL = 1,000 mg/kg/day
Reference:	ECHA, 2023

Oral Acceptable Exposure Level and PDE:

Oral Calculations	
PoD	1,000 mg/kg/day
BW	50 kg
F1 (rat)	5
F2 (intra-species variability)	10
F3 (PoD study duration: 90 days)	1 for Acute Acceptable Exposure Level
	5 for Chronic PDE
F4 (no severe toxicity)	1
F5 (NOAEL)	1
F6 (PoD route extrapolation)	Not applicable
F7 (read across)	Not applicable
Acute Acceptable Exposure Level = 1,000 mg/kg/day x 50 kg / (5 x 10 x 1 x 1 x 1) = 1,000 mg x 1000 µg/mg = **1,000,000 (µg/day)**	
Chronic PDE = 1,000 mg/kg/day x 50 kg / (5 x 10 x 5 x 1 x 1) = 200 mg x 1,000 µg/mg = **200,000 (µg/day)**	

Parenteral Acceptable Exposure Level and PDE:

In the absence of parenteral administration repeat dose toxicity studies, the oral PoD study was used to derive the parenteral PDE with the inclusion of a bioavailability modifying factor (F6) based on physiochemical characteristics of erucamide (MW = 337.6 g/mol and predicted LogP 8.8). Therefore, an F6 of 10 is applied.

Parenteral Calculations	
PoD	1,000 mg/kg/day
BW	50 kg
F1 (rat)	5
F2 (intra-species variability)	10
F3 (PoD study duration: 90 days)	1 for Acute Acceptable Exposure Level
	5 for Chronic PDE
F4 (no severe toxicity)	1

F5 (NOAEL)	1
F6 (Physicochemical characteristics)	10
F7 (read across)	Not applicable
Acute Acceptable Exposure Level = 1,000 mg/kg/day x 50 kg / (5 x 10 x 1 x 1 x 1 x 10) = 100 mg x 1000 µg/mg = **100,000 (µg/day)**	
Chronic PDE = 1,000 mg/kg/day x 50 kg / (5 x 10 x 5 x 1 x 1 x 10) = 20 mg x 1,000 µg/mg = **20,000 (µg/day)**	

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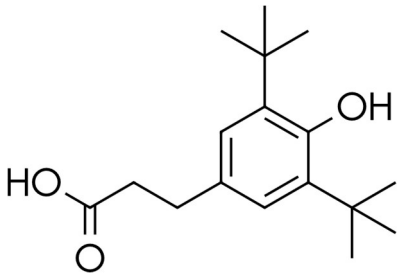
3-(3,5-Di-tert-butyl-4-hydroxyphenyl) propanoic acid (Irganox 1310)



Summary Acute Acceptable Exposure Levels and Chronic PDEs for Irganox 1310 (CAS# 20170-32-5)

Irganox 1310		
Administration Route	**Oral (µg/day)**	**Parenteral (µg/day)**
Acute*	**300,000**	**300,000**
Chronic	**30,000**	**30,000**

*Acute Acceptable Exposure Level is applicable to ≤1-month daily administration

Introduction

3,5-Di-tert-butyl-4-hydroxyphenylpropionic acid (tradename: Irganox 1310) is a phenylpropanoic acid and a hydrolysis degradation product of the antioxidant pentaerythritol tetrakis(3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate (tradename: Irganox 1010). Irganox 1010 is commonly added to polymeric materials used for pharmaceutical packaging components/systems, such as medical infusion bags, to enhance stability and prevent aging. Irganox 1310 has been observed as a leachable associated with pharmaceutical manufacturing and packaging components/systems (Zhang F et al, 2016; Tao B et al 2020).

Safety Summary

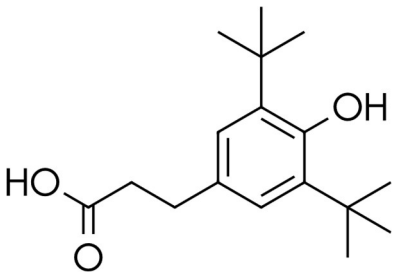
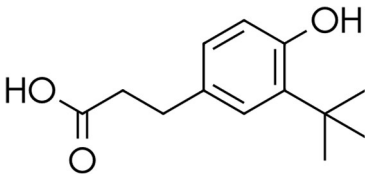
Toxicity	Yes	No
Mutagenicity*		X
Extreme or strong potency skin sensitizer*		X
Skin and eye irritation*	X (phenol structural group)	
Systemic toxicity**		X

* Based on in silico prediction

** Based on surrogate structure repeat dose toxicity data

No toxicity studies available with Irganox 1310; however, studies are available for close structural analog 3-(3-tert-butyl-4-hydroxyphenyl)propionic acid, with a Tanimoto similarity score of 98.5% (PubChem, 2024; REACH, 2014). 3-(3-tert-butyl-4-hydroxyphenyl)propionic

acid has one less tertiary butyl group than Irganox 1310 which is expected to decrease steric hindrance resulting in a more reactive phenol. No additional modifying factor was deemed necessary.

	Leachable	Surrogate
Name	**3,5-Di-tert-butyl-4-hydroxyphenylpropionic acid (Irganox 1310)**	**3-(3-tert-butyl-4-hydroxyphenyl)propanoic acid**
Structure		
CAS#	20170-32-5	107551-67-7
Molecular weight (g/mol)	278.4	222.28
Log P	4.7	3

Limiting Toxicity for Surrogate

Basis for Acceptable Exposure and PDE	
PoD Study:	OECD 407 compliant 28-day oral gavage toxicity study
Species:	Rat
Doses:	10, 50 and 300 mg/kg/day
Observations and Limiting Toxicity:	No adverse treatment-related effects were observed at any dose
PoD:	NOAEL = 300 mg/kg/day
Reference:	REACH, 2014

Oral Acceptable Exposure Level and PDE:

Oral Calculations	
PoD	300 mg/kg/day
BW	50 kg
F1 (rat)	5
F2 (intra-species variability)	10
F3 (PoD study duration: 28 days)	1 for Acute Acceptable Exposure Level
	10 for Chronic PDE
F4 (no severe toxicity)	1
F5 (NOAEL)	1
F6 (PoD route extrapolation)	Not applicable
F7 (surrogate selection)	1

Acute Acceptable Exposure Level = 300 mg/kg/day x 50 kg / (5 x 10 x 1 x 1 x 1 x 1) = = 300 mg x 1,000 µg/mg = **300,000 (µg/day)**
Chronic PDE = 300 mg/kg/day x 50 kg / (5 x 10 x 10 x 1 x 1 x 1) = 30 mg x 1,000 µg/mg = **30,000 (µg/day)**

Parenteral Acceptable Exposure Level and PDE:

In the absence of parenteral administration repeat dose toxicity studies, the oral POD study was used to derive the parenteral PDE with the inclusion of a bioavailability modifying factor (F6). In silico predictions of absorption and oral bioavailability are 100% and 95.6%, respectively.

Parenteral Calculations	
PoD	300 mg/kg/day
BW	50 kg
F1 (rat)	5
F2 (intra-species variability)	10
F3 (PoD study duration: 28 days)	1 for Acute Acceptable Exposure Level
	10 for Chronic PDE
F4 (no severe toxicity)	1
F5 (NOAEL)	1
F6 (physicochemical characteristics)	1
F7 (surrogate selection)	1
Acute Acceptable Exposure Level = 300 mg/kg/day x 50 kg / (5 x 10 x 1 x 1 x 1 x 1 x 1) = 300 mg x 1000 µg/mg = **300,000 (µg/day)**	
Chronic PDE = 300 mg/kg/day x 50 kg / (5 x 10 x 10 x 1 x 1 x 1 x 1) = 30 mg x 1000 µg/mg = **30,000 (µg/day)**	

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OECD QSAR Toolbox. Version 4.5 SP1. Prediction results of 3-(3,5-Di-tert-butyl-4-hydroxyphenyl) propanoic acid (CAS 20170-32-5) for profilers: “Eye irritation/corrosion Inclusion rules by BfR” and “Skin irritation/ corrosion Inclusion rules by BfR”. Predictions performed: 1-25-25.

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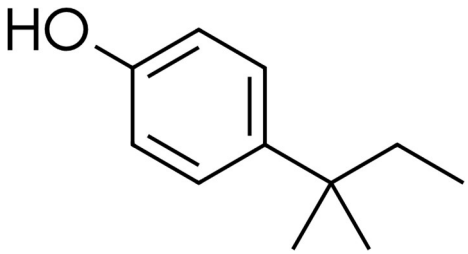
4-Tert-Amylphenol



Summary Acute Acceptable Exposure Levels and Chronic PDE Values for 4-Tert-Amylphenol (CAS# 80-46-6)

4-Tert-Amylphenol		
Administration Route	**Oral (µg/day)**	**Parenteral (µg/day)**
Acute*	**50,000**	**25,000**
Chronic	**5,000**	**2,500**

* Acute Acceptable Exposure Level is applicable to ≤1-month daily administration

Introduction

4-Tert-Amylphenol is an alkylated phenol and used as an antimicrobial in cleaning agents, as well as an antioxidant and UV stabilizer in synthetic rubber, plastic materials, and resin manufacturing (PubChem, 2024; AICIS report, 2021). It has been observed and reported as a leachable from packaging components/systems.

Safety Summary

Toxicity	Yes	No
Mutagenicity		X
Extreme or strong potency skin sensitizer		X
Skin and eye irritation	X	
Systemic toxicity	X 10-50% bodyweight gain reduction	

4-Tert-Amylphenol is a known environmental endocrine disruptor, not human health, and therefore this endpoint is not considered as the limiting toxicity (ECHA, 2021).

Limiting Toxicity

Basis for Acceptable Exposure and PDE	
PoD Study:	Oral prenatal developmental toxicity study
Species:	Rat
Doses:	0, 50, 200, and 500 mg/kg/day from gestation days 6 to 15
Observations and Limiting Toxicity:	Maternal toxicity ≥200 mg/kg/day (increased incidence of hair loss, urine stains, abnormal respiratory sounds, soft stools, along and 10–50% decrease in body weight gain and food consumption). At 500 mg/kg/day, fetal effects secondary to maternal toxicity (bent ribs and 6% decrease in fetal body weight)
PoD:	NOAEL for maternal toxicity was 50 mg/kg/day, and for developmental toxicity, it was 200 mg/kg/day
Reference:	EA, 2008; AICIS, 2021

Oral Acceptable Exposure Level and PDE:

Oral Calculations	
PoD	50 mg/kg/day
BW	50 kg
F1 (rat)	5
F2 (intra-species variability)	10
F3 (PoD study duration: gestation days 6 to 15)	1 for Acute Acceptable Exposure Level
	10 for Chronic PDE
F4 (no severe toxicity)	1
F5 (NOAEL)	1
F6 (PoD route extrapolation)	Not applicable
F7 (read across)	Not applicable
Acute Acceptable Exposure Level = 50 mg/kg/day x 50 kg / (5 x 10 x 1 x 1 x 1) = 50 mg x 1,000 µg/mg = **50,000 (µg/day)**	
Chronic PDE = 50 mg/kg/day x 50 kg / (5 x 10 x 10 x 1 x 1) = 5 mg x 1,000 µg/mg **= 5000 (µg/day)**	

Parenteral Acceptable Exposure Level and PDE:

In the absence of parenteral administration repeat dose toxicity studies, the oral PoD study was used to derive the parenteral values with the inclusion of a bioavailability modifying factor (F6). In silico prediction of absorption and oral bioavailability, are as 100% and 61.7%, respectively. Therefore, an F6 of 2 is applied.

Parenteral Calculations	
PoD	50 mg/kg/day
BW	50 kg
F1 (rat)	5

F2 (intra-species variability)	10
F3 (PoD study duration: gestation days 6 to 15)	1 for Acute Acceptable Exposure
	10 for Chronic PDE
F4 (no severe toxicity)	1
F5 (NOAEL)	1
F6 (bioavailability: predicted)	2
F7 (read across)	Not applicable
Acute Acceptable Exposure = 50 mg/kg/day x 50 kg / (5 x 10 x 1 x 1 x 1 x 2) = 25 mg x 1,000 µg/mg **= 25,000 (µg/day)**	
Chronic PDE = 50 mg/kg/day x 50 kg / (5 x 10 x 10 x 1 x 1 x 2) = 2.5 mg x 1,000 µg/mg = **2500 (µg/day)**	

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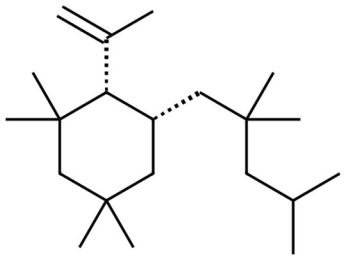
Candidate List of substances of very high concern for Authorisation (published in accordance with Article 59(10) of the REACH Regulation) https://echa.europa.eu/candidate-list-table/-/dislist/details/0b0236e180e22a96

Australian Industrial Chemicals Introduction Scheme (AICIS), Phenol, 4-(1,1-dimethylpropyl)- (4-tertpentylphenol), Evaluation statement. September 14, 2021.

cis-1,1,5,5-Tetramethyl-2-(1-methylethenyl)-3-(2,2,4-trimethylpentyl)-cyclohexane (Rubber Oligomer $C_{21}H_{40}$)



Summary Acute Acceptable Exposure Levels and Chronic PDEs for (Rubber Oligomer $C_{21}H_{40}$) (CAS# 114123-73-8)

(Rubber Oligomer $C_{21}H_{40}$)		
Administration Route	**Oral (µg/day)**	**Parenteral (µg/day)**
Acute*	**100,000**	**10,000**
Chronic	**10,000**	**1,000**

*Acute value is applicable to ≤1-month daily administration

Introduction

Cis-1,1,5,5-Tetramethyl-2-(1-methylethenyl)-3-(2,2,4-trimethylpentyl)-cyclohexane (also known as rubber oligomer $C_{21}H_{40}$) belongs to the class of organic compounds known as sesquiterpenoids. These are terpenes with three consecutive isoprene units (Feunang et al, 2016). Rubber oligomer $C_{21}H_{40}$ is an oligomer for the preparation of butyl rubber and in the copolymerization of isoprene (Chemical Book, 2023). Rubber oligomer $C_{21}H_{40}$ is observed as a leachable or extractable associated with rubber pharmaceutical manufacturing and packaging components.

Safety Summary

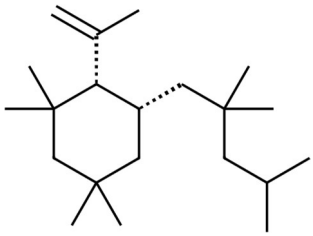
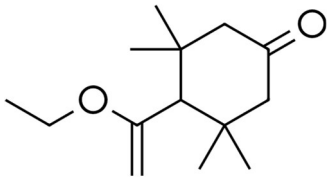
Toxicity	Yes	No
Mutagenicity*		X
Extreme or strong potency skin sensitizer*		X
Skin and eye irritation*		X
Systemic toxicity**		X

* Based on in silico prediction

** Based on surrogate structure repeat dose toxicity data

There were no systemic toxicity studies available with rubber oligomer $C_{21}H_{40}$; however, studies were available for the structural analog 3,3,5,5-tetramethyl-4-ethoxyvinylcyclohexanone determined using the US EPA Analog Identification Methodology

(AIM, 2025) and is chosen as a surrogate for PDE derivation. Based on the physicochemical characteristics of MW and Log P presented below, a route extrapolation from oral to parenteral exposure modifying factor F6 = 10 was applied. No additional modifying factor was deemed necessary for the surrogate structure selection for read across.

	Leachable	Surrogate
Name	**Rubber Oligomer $C_{21}H_{40}$**	**3,3,5,5-tetramethyl-4-ethoxyvinylcyclohexanone**
Structure		
CAS#	**114123-73-8**	**36306-87-3**
Molecular weight (g/mol)	**292.5**	**224.34**
Log P	**8.8**	**3.1**

Limiting Toxicity for Surrogate

Basis for Acceptable Exposure and PDE	
PoD Study:	OECD 422 compliant dietary combined repeated dose toxicity study with reproduction/developmental toxicity screening test
Species:	Rat
Doses:	1,500, 5,000 and 15,000 ppm or 97, 323, 970 mg/kg/day. Males exposed for 2 weeks prior to mating, d0uring mating, and up to termination (total 29 days). Females exposed for 2 weeks prior to mating, during mating, during post-coitum, and during at least 4 days of lactation (total 41–47 days)
Observations and Limiting Toxicity:	Kidney (macroscopic and histological correlates of hyaline droplet accumulation and granular casts), liver (macroscopic findings and hepatocellular hypertrophy), spleen (absolute and relative weight), as well as decreased food consumption and body weight
PoD:	NOAEL = 97-103 mg/kg/day
Reference:	Api et al, 2021

Oral Acceptable Exposure Level and PDE:

Oral Calculations	
PoD	100 mg/kg/day
BW	50 kg
F1 (rat)	5
F2 (intra-species variability)	10
F3 (PoD study duration: 29 days)	1 for Acute Acceptable Exposure Level
	10 for Chronic PDE
F4 (no severe toxicity)	1
F5 (NOAEL)	1
F6 (PoD route extrapolation)	Not applicable
F7 (surrogate selection)	1
Acute Acceptable Exposure Level = 100 mg/kg/day x 50 kg / (5 x 10 x 1 x 1 x 1 x 1) = = 100 mg x 1,000 µg/mg = **100,000 (µg/day)**	
Chronic PDE = 100 mg/kg/day x 50 kg / (5 x 10 x 10 x 1 x 1 x 1) = 10 mg x 1,000 µg/mg = **10,000 (µg/day)**	

Parenteral Acceptable Exposure Level and PDE:

In the absence of parenteral administration repeat dose toxicity studies, the oral POD study was used to derive the parenteral PDE with the inclusion of a bioavailability modifying factor (F6). In silico predictions of absorption and oral bioavailability are 100% and 95.6%, respectively.

Parenteral Calculations	
PoD	100 mg/kg/day
BW	50 kg
F1 (rat)	5
F2 (intra-species variability)	10
F3 (PoD study duration: 29 days)	1 for Acute Acceptable Exposure Level
	10 for Chronic PDE
F4 (no severe toxicity)	1
F5 (NOAEL)	1
F6 (physicochemical characteristics)	10
F7 (surrogate selection)	1
Acute Acceptable Exposure Level = 100 mg/kg/day x 50 kg / (5 x 10 x 1 x 1 x 1 x 10 x 1) = 100 mg x 1,000 µg/mg = **10,000 (µg/day)**	
Chronic PDE = 100 mg/kg/day x 50 kg / (5 x 10 x 10 x 1 x 1 x 10 x 1) = 100 mg x 1,000 µg/mg = **1,000 (µg/day)**	

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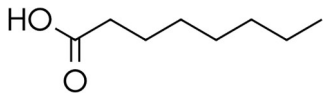
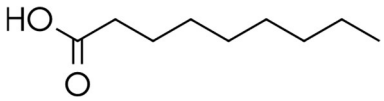
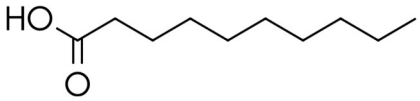
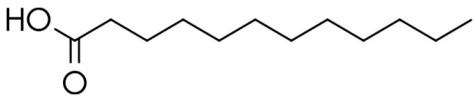
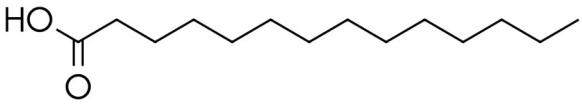
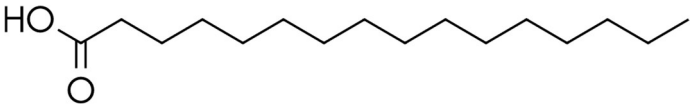
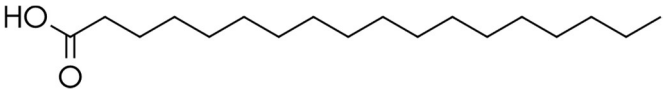
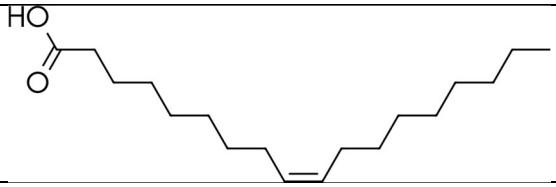
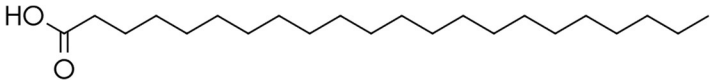
Common Fatty Acid Leachables (C12-C22)

Chemical Name (CAS#)	**Structure**
Caprylic acid (C8) 124-07-5	
Nonanoic acid (C9) 112-05-0	
Capric acid (C10) 334-48-5	
Lauric acid (C12) 57-10-3	
Myristic acid (C14) 544-63-8	
Palmitic acid (C16) 57-10-3	
Stearic acid (C18) 57-11-4	
Oleic acid (C18) 112-80-1	
Docosanoic acid (C22) 112-85-6	

Introduction

Fatty acids are generally defined as having a carboxylic acid with a long, unbranched aliphatic chain that typically consists of an even number of carbon atoms. The aliphatic chain may be saturated (i.e., only single bonds between carbon atoms), monounsaturated (i.e., containing one double bond), or polyunsaturated (i.e., containing two or more double bonds). This monograph covers unsaturated and monosaturated fatty acids with chain length C8 to C22. Fatty acids are endogenous substances and ubiquitous in the diet. Fatty acids are also commonly used as raw materials for pharmaceutical manufacture and observed as leachables and extractables from packaging components/systems (Jolly et al, 2022).

Free fatty acids may be present in total parenteral nutrition solutions and intravenous lipid emulsions. Finally, lauric, myristic, palmitic, stearic, and oleic acids are Generally Recognized

as Safe and/or components of GRAS substances following oral exposure (U.S. FDA, 2018) and, except for lauric acid, listed in the FDA inactive ingredient database as being present in approved drug products (various administration routes and dosage forms). Stearic acid is also included by the Council of Europe (1974), at a level of 4000 ppm, in the list of artificial flavouring substances that may be added to foodstuffs without hazard to public health.

Safety Summary

Available data indicate fatty acids C8-C22 are of low to moderate acute toxicity; not mutagenic; not skin sensitizers and not irritating to the skin and eyes of rabbits. Key repeat dose toxicity studies are summarized below.

Toxicity Study Summary Nonanoic acid (C9)	
Study:	OECD 407 and GLP compliant 28-day oral toxicity study
Species:	Rat
Doses:	50, 100 and 1,000 mg/kg/day
Observations and Limiting Toxicity:	No adverse systemic toxicity effects were observed
NOAEL:	1,000 mg/kg/day
Reference:	Api et al, 2020

Toxicity Study Summary Docosanoic acid (C22)	
Study:	OECD 422 compliant oral combined repeated dose toxicity study with reproduction/developmental toxicity screening test
Species:	Rat
Doses:	100, 300 and 1,000 mg/kg/day
Observations and Limiting Toxicity:	No adverse toxicity effects were observed
NOAEL:	1,000 mg/kg/day (systemic and reproductive/developmental toxicity)
Reference:	Nagao et al, 2002

Fatty acids share a common degradation pathway and are metabolized to acetyl-Coenzyme A (acetyl-CoA) or other key metabolites that are structurally similar breakdown products. No significant differences in metabolic clearance are expected between different carbon chain lengths, saturated and unsaturated compounds, or branched chain compounds, although **different reaction sequences accommodate different structures (CIR, 2019).**

Jolly et al (2022) reviewed the available toxicity data of eight fatty acids (including palmitic, stearic, lauric and oleic acid) and proposed parenteral health-based exposure limits (Jolly et al, 2022). Key considerations were based on clinical parenteral exposure and potential for micelle forming capacity and low-density lipoprotein levels with concomitant increased risk of cardiovascular disease. A parenteral chronic class-specific value of 50 mg/day was proposed

and considered applicable to multiple fatty acids exposure, including fatty acids lacking toxicity data.

Acceptable Exposure for Unsaturated or Monosaturated Fatty Acids C8 to C22

Based on endogenous and exogenous human exposure, as well as non-clinical exposure, fatty acids are considered to be of low acute and chronic toxicity. Aligned with product quality considerations, systemic exposure of ≤10 mg/day to one or more C8 to C22 fatty acids is acceptable without justification regardless of the administration route or exposure duration. Higher amounts may also be acceptable with appropriate justification.

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国际人用药品注册技术协调会

ICH 协调指导原则

可提取物与浸出物指导原则
Q3E

草案

于 2025 年 8 月 1 日签署

目前正在公开征求意见

在 ICH 进程的第 2 阶段，ICH 大会按照国家或地区程序，将相应 ICH 专家工作组商定的共识草案文本或指导原则转交给 ICH 地区的监管机构，供内部和外部征求意见。

ICH Q3E

文件历史

编码	历史	日期
Q3E	在第 2a/b 阶段中获得 ICH 大会监管成员批准，发布以公开征求意见。	2025 年 8 月 1 日
Q3E 支持性文件	在第 2a/b 阶段中获得 ICH 大会监管成员批准，与 ICH Q3E: 可提取物与浸出物指导原则一起发布以公开征求意见。	2025 年 8 月 1 日

ICH协调指导原则

可提取物与浸出物指导原则

Q3E

ICH 协调指导原则

目录

1. 前言

浸出物是指在既定的生产和标示的贮藏条件下，从生产组件/系统、包装或给药装置的组件迁移至药品中的化学物质。可提取物是指在特定的实验室试验条件下，从生产组件/系统、包装或给药装置的组件中有意提取的化学物质，这些化学物质是潜在的浸出物。

本指导原则为浸出物的评估和控制提供了一个整体的框架和流程，进一步扩展了现有ICH 关于杂质的指导原则，包括新原料药（ICH Q3A）和新药制剂（ICH Q3B）中的杂质、残留溶剂（ICH Q3C）和元素杂质（ICH Q3D），以及 DNA 反应性（致突变）杂质（ICH M7）。本指导原则的框架遵循 ICH Q9 中描述的风险管理原则。本指导原则涉及了材料表征和工艺理解的内容，然而其主要目的是通过评估和控制药品中的浸出物来保障患者安全和产品质量。由于材料工程、新装置、新生产模式和新型治疗方式的快速发展，本指导原则主要在科学和监管领域内提供前瞻性的原则和概念。

2. 适用范围

本指导原则适用于新的药物制剂（包括细胞和基因治疗产品）中浸出物的风险评估和控制。需要上市许可且符合化学药品或生物制品定义的药械组合产品同样在本指南的适用范围内。

本指导原则主要关注有机浸出物。尽管元素杂质分析的推荐方法包含在本指导原则的范围内，但元素杂质浸出物的安全性评估应参照 ICH Q3D，因此不在此指导原则的适用范围内。

本指导原则同样适用于已批准产品中可能影响浸出物谱或患者暴露量的变更，例如涉及处方、生产工艺、给药剂量和（或）包装系统的变更（即，生命周期管理）。本指导原则不适用于产品因污染或掺假而引入的外源性物质、外来物质或异物。

本指导原则不适用于草药、动物或植物来源的粗制品。对于这些液体剂型的产品，可适用区域性的要求。

本指导原则不适用于临床研究阶段使用的产品。然而，当患者存在高风险的情况下，可

采用本指导原则的总体原则来支持临床研究。

原则上，除特殊考虑外，放射性药物不在本指导原则的适用范围内。

本指导原则不适用于辅料的生产或贮藏。关于液体或半固体活性药物成分（APIs）包装组件的特殊考虑，请参见第 3.4.1 节。

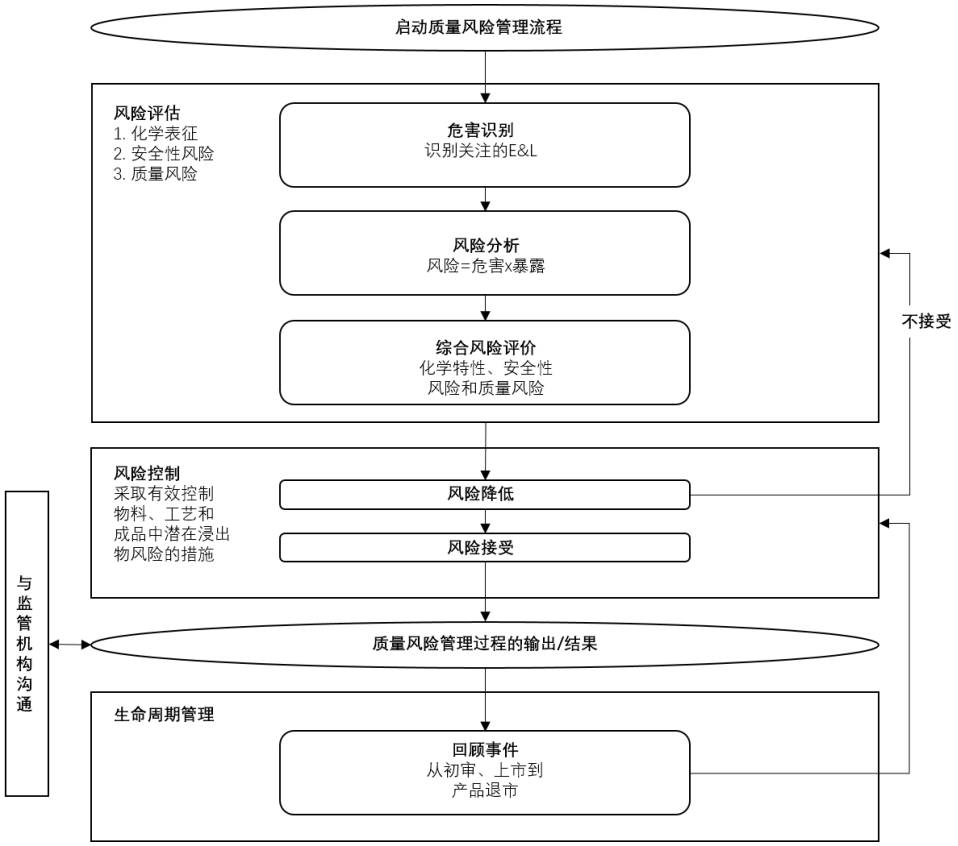
3. 可提取物和浸出物的风险评估与控制

3.1 总体原则

本指南旨在构建一个整体的框架，以识别、评估和控制与浸出物相关的风险，从而确保药品的安全性、有效性和质量属性满足要求。图 1 目的是为产品开发过程中的相关考量提供指导，这些考量贯穿于产品注册前的阶段以及整个生命周期管理过程中的持续性质量管理环节。

图 1：风险管理流程概述

（E&L = 可提取物与浸出物）



可提取物与浸出物（E&L）的质量风险管理流程需要制定全面的策略。该策略应充分运

用先验知识，并且深入理解生产/包装组件以及药品的目标属性和关键属性，同时还需充分考虑药品的生产工艺和储存条件。分析化学与安全评估方面专家之间的密切合作对于知识共享以及 E&L 质量风险管理流程的开发至关重要。每个产品都应启动一个质量风险管理流程，包括其各自的风险评估、风险控制以及生命周期管理流程。

3.2 多因素风险矩阵的概念

在进行浸出物的总体风险评估和控制时，必须充分考虑风险的多维度特性，既涵盖药品质量方面，也包括安全性方面。就药品质量而言，关键考量维度包括:

- 生产设备或包装组件与处方之间相互作用的可能性，
- 可能导致产生浸出物的设备或组件的理化性质，以及使用前对组件的预处理，
- 生产和贮藏条件，包括但不限于表面积与溶液体积比、温度、接触时间、下游去除步骤的邻近程度及其去除潜在浸出物的能力。
- 处方的浸出倾向，包括但不限于 API、pH 值、有机共溶剂和表面活性剂/螯合剂等。

安全性评估维度与浸出物可能引发的危害相关，包括与暴露相关的多种因素，例如: 给药途径、相关患者人群、最大给药剂量、给药频率和/或给药间隔，以及终生累计最大治疗时间等。

图 2 展示了不同维度（未包含全部）的相对风险。药品浸出物的总体风险是综合考虑所有维度来确定的。

图 2：风险矩阵考量维度概述

CSF=脑脊液；DP=制剂；IM=肌肉；IV=静脉；SC=皮下

根据预期的风险并运用先验知识，可采用多种方法来进行风险评估和控制，包括从相关食品接触安全或药典标准/法规的符合性，到更全面的 E&L 表征和安全性风险评估（参见附录 1）。对于口服制剂，当进行充分论证后（如，拟定用途符合区域食品接触相关法规，药物制剂的浸出倾向与所参考区域法规中所列举的情形相似或更低，且所有特定的测试结果均符合可接受标准），符合相关区域食品接触的安全法规可能足以支持聚合物生产设备/系统及包装系统的安全性和质量。

对于其他剂型，或成分、质量标准和使用限制不符合食品接触法规要求的口服制剂，通常需进行可提取物/浸出物评估。

上述风险矩阵及风险因素突显了浸出物相关风险评估的复杂性。了解各相关因素的风险水平是风险评估过程的一部分，并有助于指导生产及包装组件的选择以及总体风险评估/控制策略的制定。

3.3 风险评估

基于风险管理流程（图 1，第 3.1 节）、多维风险矩阵（图 2，第 3.2 节）以及 E&L 风险评估和风险控制的典型工作流程（图 3 和 4，附录 1）的描述，风险评估可以概括为以下三个基本步骤:

- 第 1 步 - 危害源识别: 基于先验知识（如组件的使用经验、既往已开展的试验等）和/或可提取物及浸出物试验，识别可能从直接接触面（如生产组件/系统、包装系统及给药装置组件）或间接接触面（如次级包装，半透性组件标签所用的油墨或粘合剂）迁移至制剂中的潜在浸出物。

- 第 2 步 - 风险分析: 量化制剂中浸出物的潜在水平以及患者的暴露量。

- 第 3 步 - 综合风险评价: 评估对产品质量、安全性和有效性的风险，以确定所选生产组件/系统和包装系统是否满足拟定用途。

3.4 风险控制

如果综合风险评估表明需要降低风险，那么可以采取的措施包括但不限于: 更换组件/供应商、对组件进行预清洗、对生产设备进行再冲洗，以及增加额外的纯化/分离步骤。应通过可提取物和/或浸出物研究来确认/验证最终实施的风险减少措施是否充分。

当组件经确认满足拟定用途后，需对其建立适当的控制策略，包括但不限于对于组件质量控制至关重要的常规 GMP 规范。控制策略应包括:

- 建立全面的质量控制，包括组件的可接受标准、分析方法和取样计划（如适用）。

- 与组件供应商签订适当的质量协议，其中应包括组件全生命周期质量控制的相关内容，特别是涉及任何可能影响可提取物谱的配方和/或生产工艺的变更。

有关 E&L 风险评估和风险控制的典型工作流程参见附录 1，包括生产组件/系统（图 3，附录 1）以及包装系统和给药装置组件（图 4，附录 1）的组件确认。通常，需要对包装和给药装置组件进行可提取物和浸出物研究。在某些特定情况下，如果理由充分，也可以提出其他替代方法。

包装和给药装置组件浸出物风险识别的原则和规范以及降低风险所采用的策略，同样适

用于与制剂相关溶液直接接触的聚合物生产设备组件。可提取物研究的设计应体现最差生产条件（例如，最小批量下最长接触时间、最高温度和压力）。通常认为由于生产组件/系统与制剂的接触时间相对较短，药液体积与组件接触的表面积比值相对较大，制剂中浸出物来源于生产组件/系统的可能性低于包装和给药系统组件。在上游生产工艺步骤中引入的浸出物也许能够通过下游步骤（例如，精制/纯化）进行清除，从而降低浸出物最终引入制剂终产品的风险。这些因素应在选择和确认生产设备以及进行质量调查时进行考虑。

对于生产组件/系统而言，如果所有可提取物的检出量均小于等于制剂的分析评价阈值（AET），并且未检出 1 类浸出物时（见第 5 节），那么其浸出物风险可被认为极低且可接受。提取研究中使用的分析方法应符合第 4.3 节中所列出的标准。

当生产组件/系统的可提取物检出量高于 AET 时，可以进行可提取物的定性鉴别和定量检测来评估浸出物风险，前提是需采用与鉴别得到的可提取物结构一致的适宜对照品进行定量检测。如果无法获得结构一致的对照品，则可使用具有相似分析响应的化合物。如果采用上述定量方法测得的可提取物浓度低于相关可接受的安全性水平（见第 6 节），则认为浸出物相关的安全性风险可忽略不计。对于生产设备中检出量大于 AET 的可提取物，也可通过进行浸出物的安全性评估这种替代方案进行确认。

对于药品包装组件/系统，如果患者安全风险可以通过先验知识进行充分控制（例如，已建立可提取物/浸出物相关性，拟申报制剂与已获批上市制剂浸出倾向相似），或未检出/检出少量大于 AET 但小于其安全性阈值的可提取物（如 3 类浸出物，参见第 6 节），则可考虑提交简化的研究数据包。表 A.1.2（附录 1）提供了与图 2（第 3.2 节）相关的总体风险较低的示例，在进行充分论证的前提下可考虑提交简化数据包。当申请提交简化数据包时，建议与相关区域监管机构/卫生监管部门进行沟通，以确认所用方法可被接受。

如果鉴别得到的可提取物可能通过化学转化（即，通过化学降解和/或与处方组分相互作用）产生安全性风险更高的化合物，或无法充分鉴别和/或定量测定大于 AET 的所有可提取物峰，则应进行浸出研究来解决这些问题并证明组件的可接受性。

3.4.1 特殊考虑

对于使用多个组件的生产工艺，尤其是那些由相同或相似材料构成的组件，应评估浸出物累积的风险。

质量风险评估及其控制策略，如适用时，还应涵盖储存液体原料药或半固体原料药容器的潜在浸出物。

尽管在冷冻状态下浸出极少，仍应评估冷冻前和解冻后包装组件/系统的潜在浸出风险。

此外，对于生物制品和生物技术衍生产品，风险识别和风险降低措施还可包括:

- 评价具有反应性的浸出物与处方组分之间潜在的相互作用，可能导致对产品质量、安全性和/或有效性产生不良影响。当发现已知的反应性浸出物对产品的关键质量属性产生影响时，应考虑化学修饰的潜在机制（例如变性、聚集或降解）。

- 对于原液的生产，浸出物可在最后一个纯化步骤中去除。因此，质量风险评估通常重点关注其后续的生产过程。

3.5 文件与合规性

注册申请应包含可提取物/浸出物研究的合理性论证、相关研究报告、超出 AET 物质的安全性评估以及必要的风险控制策略。为支持生产和包装组件/系统的可接受性而进行的可提取物和浸出物研究应包含在申报资料中（如 ICH M4Q 所述）。应提供充分的浸出物数据，以确保制剂在整个货架期内的安全性和质量满足要求。通常情况下，可以与已有的稳定性数据一并提交浸出物研究结果，在事先征得相关区域监管部门同意后，可在批准后提交额外数据。应按照本指导原则第 3.3 节相关内容，对一次性使用和多次使用的生产组件/系统、初级包装组件和给药装置组件进行质量风险评估。对于半渗透性包装材料，还应视情况对次级包装进行评估。

应提供可提取物研究和浸出物研究资料，以及相应的评估报告，报告中通常应包括可提取物研究所用的分析方法和提取条件（溶剂、温度、时间、表面积/体积比等）的选择依据，以及浸出物研究中样品制备方法以及分析方法。此外，应提供定量分析方法以及方法适用性研究（例如，检测限（LOD）、定量限（LOQ）、专属性、线性、精密度、准确度和重复性）。申报资料中应提供所有大于 AET（见第 5 节）的可提取物和浸出物的信

息，包括化学名称、结构、CAS 登记号（如有）和观察到的检出水平。对于浸出物（或用于组件/系统确认而测定的可提取物），应包括第 6 节所述的安全风险评估。

除质量风险评估外，申报资料中还应酌情提供浸出物与可提取物的相关性内容（参见第 4.6 节）。最后，应提供实施前后收集的数据来证明风险降低措施（例如包装和给药组件/系统的预清洗或生产组件/系统的再冲洗）的合理性。

3.6 风险回顾/生命周期管理

本节描述了在药品生命周期内可能需要对浸出物谱进行重新评价的变更类型。以下是潜在变更的非详尽列表，以及这些变更对患者浸出物暴露水平潜在影响的说明。因此，可能需要基于新的研究和/或现有信息对这些变更进行考量和科学论证。

新信息：如果与材料适用性相关的新数据和/或信息表明存在潜在风险，和/或如果获得了关于某浸出物的新的患者安全性信息，则可能需要更新评估。

制剂处方的变更：制剂的变更可能导致现有与制剂直接接触的生产组件/系统，和/或直接接触的包装，和/或给药装置组件引入的浸出物发生变化。例如，辅料/表面活性剂组成或浓度的变更可能影响浸出物的种类和含量。

与原料药和/或制剂直接接触的包装系统、给药装置或生产组件/系统的变更：在药品有效期内，当与原料药（主要是液体和/或生物制品）或制剂直接接触的材料在配方、供应商、生产工艺、几何构造或预处理等方面发生变更时，浸出物谱可能改变。此外，对于某些产品，其非直接接触的包装组件也可能引入潜在浸出物。

生产工艺的变更：工艺条件的变更可能导致现有制剂直接接触的材料引入不同的浸出物或导致浸出物含量发生改变。例如，溶剂体系、接触时间、温度、压力、pH 值、清洗/灭菌工艺、表面积/体积比、操作前准备（如冲洗）等条件的变更，可能影响浸出物的组成和含量。

可能影响患者暴露量的变更：药物的剂量方案、治疗持续时间、给药途径和患者人群（如，老年患者/儿童患者）等变更，均可能改变患者对先前已知浸出物的暴露量评估值。所有这些变更均可能影响浸出物暴露量评估和毒理学风险评估中所依据的基本前提。

可能影响患者获益风险比的适应症变更：例如，适应症由抗肿瘤变更为风湿免疫疾病。

4. 化学试验和评估

4.1 先验知识

先验知识可包括在进行化学试验之前需获取的有用信息，包括供应商提供的信息以及其他制剂产品和生产工艺的相关信息。这些信息可能包括:

- 配方（例如，基础聚合物和共聚物、各添加剂，如增塑剂、加工助剂、催化剂、抗氧剂）
- 食品接触合规性
- 无有意添加特定（如，未经授权）化合物的声明
- 药典检测
- 可用的可提取物研究
- 生物反应性试验
- 加工或预处理步骤（如，灭菌、清洁、冲洗、硅化、表面处理）
- 既往使用历史，包括其他类似制剂、生产工艺和/或接触条件的历史使用情况

4.2 组件选择

药品生产商需负责制定符合监管预期的药品生产、包装、储存和递送等相关要求，以向特定患者群体提供安全、有效的药品。特定材料或组件的浸出物风险水平与剂型相互作用的可能性相关。例如，与浸出倾向较高的剂型（如液体）相互作用的组件，其风险可能高于与浸出倾向极低的剂型（如非冻干固体）相互作用的组件。可通过从供应商处获得的信息（例如，可提取物报告、药典要求符合性等），或补充适宜的额外试验，来进行风险评估以及可提取物/浸出物研究开发，从而证明组件选择的合理性。可提取物、浸出物和模拟浸出物研究的总结见表 A.2.1（附录 2）。

4.3 可提取物研究

可提取物研究是从受试物中提取化学实体的过程。合理的可提取物研究采用的溶剂及提取条件需与制剂在最差生产或放置条件下的预期浸出倾向相关，并采用多种互补分析技术建立全面的提取物特性。合理的可提取物研究关键特性包括:

- 建立和应用制剂特定的 AET，用于指明需进行鉴定并作为潜在浸出物处理的可提取化学实体。对组件或组装系统进行测试，包含可代表最终成品组件或系统使

用的加工和处理操作（如，灭菌、成型与制造条件、清洁、硅化）。

- 选择适宜的提取介质，包括与制剂处方相关且具有代表性的不同 pH 值和极性的溶剂（如辅料、表面活性剂）。
- 代表制剂在生产过程中，或包装组件/系统在货架期内最差条件下（例如，接触面积、温度、持续时间）可能产生的浸出物。
- 所采用的分析方法在与提取研究目的相适应的水平上进行充分确认。
- 包括针对挥发性、半挥发性和非挥发性有机可提取物及元素可提取物的适宜分析方法。
- 可提取物报告详细描述分析方法的内容。

根据对结构材料和质量的理解，应对潜在 1 类浸出物（参见第 6.2 节“浸出物分类”）进行特定目标检测，酌情开展风险分析。对潜在 1 类浸出物的分析应遵循定量可提取物研究（第 4.3.2 节）或浸出物研究（第 4.4 节）的描述。

4.3.1 半定量可提取物研究

半定量可提取物研究可适用于随后将进行浸出物研究，以确定材料在预期用途中可接受性的情形。半定量可提取物研究的目的是确定哪些可提取物可能作为浸出物存在于制剂中。半定量可提取物研究的关键特点包括:

- 分析方法需采用若干分析中常见的可提取物或浸出物相关对照品进行确认。
- 在计算制剂特定 AET 时，使用分析不确定因子（UF; 第 5.1 节）。
- 采用相关的对照品进行可提取物的定量。

半定量可提取物如大于 AET，则可作为后续定量可提取物研究或浸出物研究的目标化合物。

4.3.2 定量可提取物研究

在半定量可提取物研究中观察到的可提取物水平高于 AET 时，如果为了确认生产组件/系统和某些低风险包装组件/系统（分别参见附录 1 表 A.1.1 和 A.1.2），则需进行定量可

提取物研究来量化这些特定的可提取物。定量可提取物研究的关键特点包括:

- 高于 AET 的可提取物需进行确定的鉴别。
- 采用分析响应相同或相似的对照品，对已鉴别的高于 AET 的可提取物进行定量测定。
- 已鉴别的高于 AET 的可提取物所用的定量分析方法应采用该特定的标准物质进行确认。

如果经充分鉴别并定量的可提取物超出其规定限度(例如，适用安全性阈值或每日允许暴露量(PDE))，则应进行浸出物研究，以证明该化合物作为浸出物时低于其规定限度。此外，当存在高于 AET 的可提取物无法进行确定性鉴别时，也可采用浸出物研究来评估其质量风险。

4.4 浸出物研究

用于支持制剂注册申报的浸出物研究旨在模拟整个拟定有效期和使用期间的实际生产条件及预期贮藏条件。在有效期内和使用期间，应评估多个时间点来表征浸出物变化趋势并估计最大检出量。在稳定性放置期间，对实际包装的制剂开展包装系统的浸出物评估，并可包括加速放置条件。对于包装系统的浸出物研究应包含采用与预期用于市售产品一致的实际包装和给药系统生产的多个制剂稳定性注册批次和/或研发批次。如果无法开展多批次研究，可提出替代方法并说明理由。在浸出物研究中使用与可提取物研究相同批次的组件可能有助于在可提取物和浸出物之间建立更有意义的相关性。应对特定目标浸出物的分析方法进行适当验证，以确认其灵敏度、专属性、准确度和精密度。还应使用非目标扫描方法，采用适当的分析技术，以检测浸出物的非预期降解、来自次级包装的浸出物和/或相互作用产物。非目标扫描方法应包含 AET 的应用（见第 5 节），即设定一个水平，高于该水平的浸出化学实体需进行鉴别、定量，并报告进行毒理学评估。

首选采用对照品（如有）进行定量，因为当用于测定适当的响应因子或标准曲线时，对照品有助于更准确和精密地定量测定目标浸出物，其可能是实际制剂中存在的浸出物；在此情况下，分析准确度和精密度较高。

4.5 模拟浸出物研究

在某些情形下，即便经过全面调查，可能包括对多种不同样本制备技术的系统研究，结合高灵敏度和高选择性的分析方法、技术及仪器设备等，仍可能在技术层面上无法进行制剂浸出物研究。此类情形可能包括与大容量注射剂（LVP）相关的检测限或定量限挑战、复杂制剂处方中固有的分析基质显著干扰，或多种此类因素叠加的情形。此时，如经过充分论证合理，使用模拟研究来支持实际制剂浸出物评价可能是可接受的。例如，可以进行模拟研究来补充浸出物研究，以完成浸出物检测中无法实现的目标。当 AET 方面存在挑战时（即分析方法 LOQ > AET），浸出物研究可使用实际可行的检测方法 LOQ 开展，并通过模拟研究填补 LOQ 与 AET 之间的差距。另外，当全面调查确认进行浸出物研究不可行时，可以使用模拟研究代替浸出物研究。

应当认识到的重要方面是，无论模拟研究的设计和执行如何完善，其结果可能仅近似于制剂浸出物研究的结果，无法完全复制制剂的真实浸出物谱。例如，模拟研究不能也不会解决浸出物与制剂处方组成之间任何潜在的相互作用问题。

模拟研究是一种替代研究，用于揭示如果进行浸出物研究，可能会检测到的潜在真实浸出物。因此，应对超过模拟研究确定的制剂特定 AET 的模拟浸出物进行鉴别、定量和安全性评估。鉴于模拟研究的目标在于获得与制剂在货架期内产生的实际浸出物谱高度相似的模拟结果，模拟研究中使用的条件与过程应与浸出物研究采用的生产/贮藏条件高度一致，以模拟制剂在生产、有效期储存及（临床）使用制备过程中经历的各项条件。此外，所选用的模拟溶剂应具有与制剂相似的浸出倾向，且模拟生产工艺还应在最差条件下实施。再者，模拟研究可基于制剂有效期放置的条件进行加速研究，从而在较短时间内模拟覆盖整个有效期的浸出物研究结果。

鉴于模拟研究旨在补充或替代浸出物研究，该研究必须满足浸出物研究的所有质量要求，包括检测方法的确认。经充分论证后，可使用模拟研究作为推荐浸出物研究的替代方法。因此，对于特定制剂开展的模拟浸出研究，其应用目的、合理性论证以及确认，应当建立在科学合理的基础上，并通过适宜的测试与试验作为全面调查的支持依据。在考虑使用模拟研究时，可能需要在实施前咨询相关区域监管机构。

4.6 可提取物和浸出物相关性

生成可提取物谱的主要目的在于表征并辅助组件选择、识别潜在浸出物、针对目标浸出

物开发检测方法，以及建立可提取物与浸出物的相关性。浸出物通常是可提取物的一个子集，在规范实施的可提取物研究中，每种浸出物的浓度通常低于相应可提取物的浓度。

当 E&L 高于 AET 时，建议评估两者之间定性和定量的相关性。当实际制剂的浸出物能与对应的组件或系统可提取物研究中的可提取物进行定性和定量比较时，也许能够建立浸出物和可提取物之间的相关性。对高风险制剂、变更控制及持续质量控制而言，如果建立了浸出物与可提取物的相关性，则在经过充分论证合理后，可采用常规组件可提取物检测代替稳定性研究期间的常规浸出物检测（如适用）。对于未检出或检出水平高于在提取研究条件下预期水平的浸出物，潜在原因可能包括：可提取物研究设计和/或执行欠佳、浸出物降解形成新化合物、浸出物与 API 和/或辅料间的相互作用产物、从包装中迁移的化学品，以及在有效期放置期间因老化（如暴露于紫外线、高温、氧气）导致材料变化产生的新浸出物。尽管 E&L 的相关性对质量风险评估具有价值和指导意义，并可能有助于组件选择和生命周期管理决策，但最终决定患者安全性风险评价和组件可接受性的仍是浸出物谱。

如果存在产品生命周期内发生的、显著改变可提取物/浸出物特征的任何变更，应快速重新评价可提取物谱/浸出物谱及其相关性。如果在制剂稳定性研究中观察到某种特定浸出物的水平明显高于预期值，（该预期值是基于提取研究计算得出的潜在最大水平，且提取研究所用的组件/系统批次与制剂稳定性批次所用批次相同），则表明提取研究不完整，可能无法就该浸出物建立有效的浸出物-可提取物相关性。

5. 分析评价阈值

AET 并非一个控制阈值，而是对应于一种浓度阈值，当可提取物或浸出物的浓度高于 AET 时，应对其进行鉴别、定量，并报告进行安全性评估，其构成了可提取物和浸出物风险评估及控制策略的基础。ICH 发布的新原料药中的杂质（ICH Q3A）和新药物制剂中的杂质（ICH Q3B）指导原则描述了一系列基于最大日剂量的预定阈值，旨在通过对关键质量属性的充分控制，确保制剂在有效期内的安全性与有效性。与上述指导原则不同，本指导原则建议采用安全性关注阈值（SCT；见第 6 节安全性评估）来首先确定相关研究特定的 AET。

可提取物研究中应包含 AET 的建立和应用，以便指明需进行检测、鉴别和报告的、可

作为制剂潜在浸出物的可提取化学实体。浸出物研究中，高于 AET 的化合物应进行鉴别和定量，以进行适当的安全性评估。对于 1 类浸出物（见附录 4 表 A.4.1），在进行定量测定时应使用化合物特定的安全性限度，而非产品特定的 SCT。

E&L 研究特定的 AET 取决于剂量相关的考量来进行确定（例如，最大剂量水平、给药频率和治疗持续时间）。根据研究类型（可提取物与浸出物）及评估内容，AET 可用不同计量单位表示。例如，溶液中可提取物的常用计量单位包括: 每克组件材料的可提取物重量（如 μg/g），或每毫升提取液体积的可提取物重量（如 μg/mL）。在浸出物研究中，可用每个包装或给药组件/系统的浸出物重量（例如，μg/组件、μg/mL、μg/g、ppm）表示基于整个包装系统或整套生产组件的浸出物 AET。无论 AET 的计量单位如何设定，均等同于某特定研究中的潜在患者等效剂量。AET 计算示例见附录 3。

5.1 分析不确定因子

当在半定量分析方法中使用 AET 时，应采用适当的不确定因子，以解决因待测物与参比对照品的响应系数差异而可能导致的待测物浓度低估问题。

在特定可提取物/浸出物研究中，适宜的分析不确定因子数值的确定需综合考虑以下因素: 对结构材料的先验知识和理解、潜在可提取物/浸出物可能的化学结构、覆盖响应因子范围的参比对照品的可及性和分析方法的局限性。

在某些情况下，可接受的方法是乘以不大于 0.5 的不确定因子（UF）。或者，可通过统计分析相关参比化合物的适当响应因子数据库来推导出不确定因子。可提取物/浸出物研究报告中应包括所应用 UF 的合理性说明。

6. 安全性评估

6.1 一般原则

必须进行基于风险的科学评价，以确认制剂中任何潜在浸出物的水平对患者构成的风险可忽略不计。在此基于风险的总体评价中，安全性评估的重点是对药物制剂中超过预定 SCT 的浸出物的毒理学评价。在此情况下，SCT 被视为一个阈值，低于该值时，浸出物的暴露水平非常低，此时其致突变和非致突变毒性问题均可忽略不计。安全性评估的结果可用于判断材料中 1 类浸出物的水平是否可接受，并可根据需要用于设定制剂中浸出

物的质量标准。

由于 SCT 旨在保护免受致突变和非致突变效应影响，故其必须同时考虑致突变性关注和替代毒性终点相关的问题，并考虑暴露方面更具限制性的因素。因此，除暴露量外，其还取决于暴露的途径和持续时间。对于致突变性问题，ICH M7 中描述的毒理学关注阈值（TTC）被视为适用。对于非致突变毒性终点，本指导原则中采用了界定限度（Qualification Threshold, QT），可将其视为潜在的非致突变毒性作用可以忽略不计的剂量。考虑到给药途径和潜在暴露持续时间，将 SCT 设定为特定制剂中 TTC 或 QT 的最低值。通过对约 330 种潜在浸出物每日允许暴露量（PDE）进行回顾，得出口服和注射给药途径的 QT 值。表 1 概述了口服、注射、经皮/透皮和吸入给药暴露途径的全身安全性阈值（μg/天）。此外，还列出了制剂中眼用局部给药、皮下/皮内、经皮/透皮和吸入给药暴露途径的浸出物浓度对应的局部毒性阈值。对于其他给药途径，本指导原则中描述的概念可用于确定可接受的暴露水平。

表 1: 全身和局部毒性阈值

<table>
<tr><th colspan="5">全身毒性阈值</th></tr>
<tr><th rowspan="2">暴露持续时间</th><th colspan="2">口服给药</th><th colspan="2">注射、经皮/透皮、吸入给药</th></tr>
<tr><th>TTC</th><th>QT</th><th>TTC</th><th>QT</th></tr>
<tr><td>>10 年</td><td>1.5 μg/天</td><td rowspan="3">48 μg/天</td><td>1.5 μg/天</td><td rowspan="3">12 μg/天</td></tr>
<tr><td>>1 至 10 年</td><td>10 μg/天</td><td>10 μg/天</td></tr>
<tr><td>>1 个月至 1 年</td><td>20 μg/天</td><td>20 μg/天</td></tr>
<tr><td>≤1 个月</td><td>120 μg/天</td><td>136 μg/天</td><td>120 μg/天</td><td>26 μg/天</td></tr>
<tr><th colspan="5">局部毒性阈值</th></tr>
<tr><th>眼用局部给药</th><th>皮下和皮内给药</th><th>经皮和透皮给药</th><th>脑内、鞘内、硬膜外和眼内给药</th><th>吸入给药</th></tr>
<tr><td>20 ppm</td><td>50 ppm</td><td>500 ppm</td><td>化合物特定评价（参见第 6.4 节）</td><td>5 μg/天</td></tr>
</table>

根据注射用 QT 确定吸入和经皮/透皮给药途径的 QT 值，以替代可用的 PDE 值。

6.2 浸出物分类

各种材料中的潜在浸出物包含多种化学物质，因此具有多种毒理学特性。为了提供一种实用的、基于风险的浸出物安全性评估方法，考虑到某些化合物具有潜在的高毒性，需将其控制在低于既定界定限度的水平。在现行指导原则中，此类化学品被归类为 1 类浸出物。对于致突变致癌物，根据 ICH M7 定义的关注队列和可接受摄入量（AI）低于 1.5 μg/天的 1 类杂质应被视为 1 类浸出物。同样，某些化合物，如双酚 A（BPA）或苯并(a)

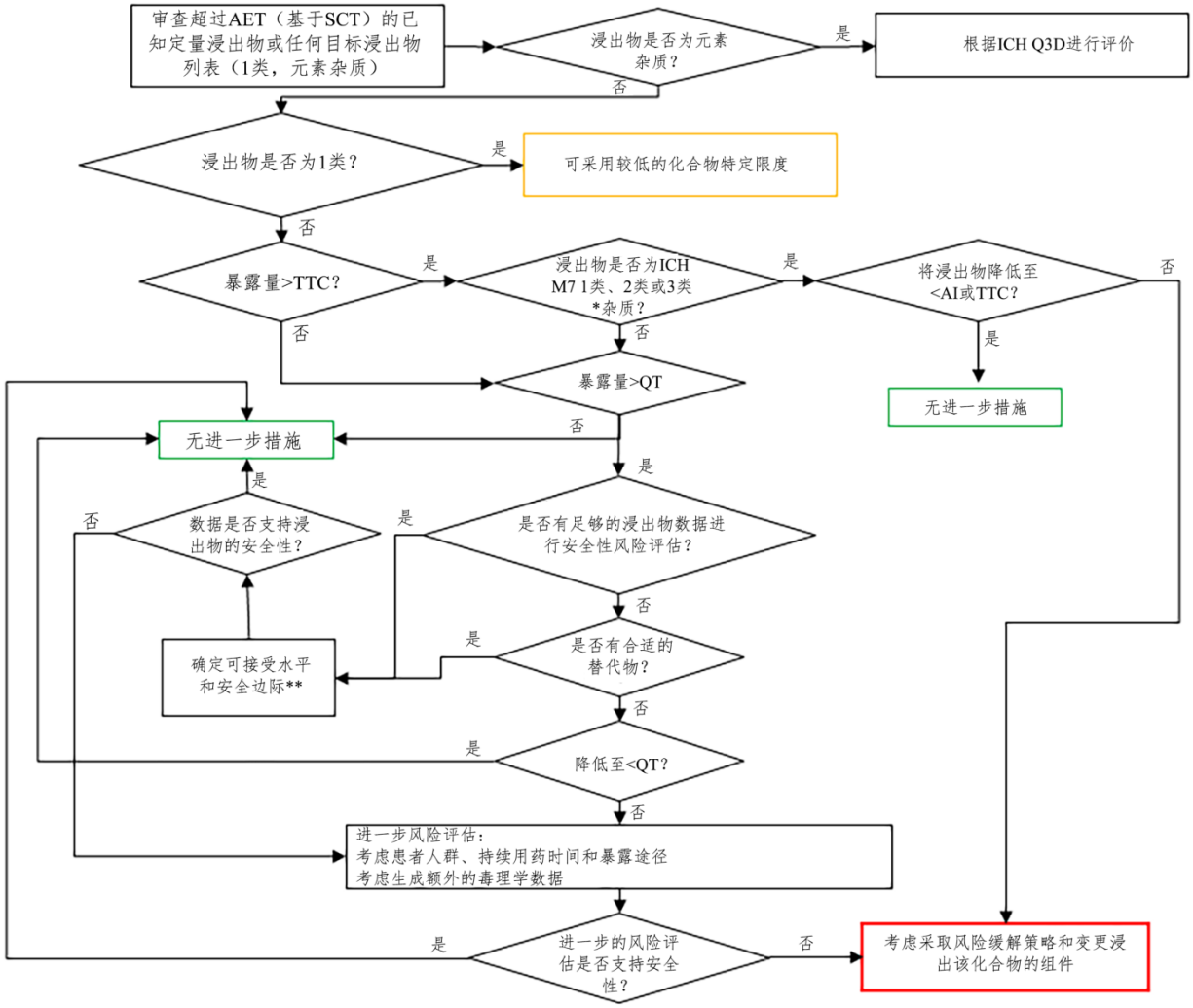
353 芘，可能具有显著的非致突变毒性风险。理论上，当制剂中这些物质的含量达到或低于
354 QT 限度值时，其带来的患者安全风险仍不可忽视。对于 1 类浸出物，最实用的做法是
355 避免使用可能浸出此类化合物的材料（见第 5 节）。然而，若此类材料或组件的使用确
356 属不可避免，则应采用针对这些物质的特定化合物安全性限度。

357 3 类浸出物是指全身毒性效力相对较低的化合物，其衍生的慢性注射 PDE 超过典型浸
358 出物水平（即应用附录 5 所述方法时，PDE≥1 mg/天）。若每日暴露水平低于 1mg/天时
359 观察到 3 类浸出物，则无需进行进一步安全性确认。介于这两类之间的是具有潜在毒性
360 的化合物，其毒性可能在浸出物的常见水平下显现（即 2 类浸出物）。附录 4 概述了这
361 三类浸出物。

362 **6.3 安全性评估流程**

363 对超过 AET 的有机浸出物，应进行鉴别、定量和报告，以供安全性风险评估。需从分
364 析角度证明对化合物结构进行部分或不完全解析的可接受性。如果毒理学上合理，在某
365 些情况下，提供暂定结构的部分解析可以为安全性评估提供依据。浸出物安全性评估的
366 一般流程见流程图（图 3），包括对致突变性和一般毒性问题的评估。

367 **图 3：使用安全性评价阈值的浸出物安全性评估流程**



*如 ICH M7 所述。

**如果浸出物的每日暴露量>1 mg/天，则应考虑进行 ICH Q3A 和 ICH Q3B 建议的遗传毒性研究（例如，细菌致突变性试验和*体外*染色体畸变试验）。

在材料和组件选择过程中，应设法识别并避免潜在的 1 类浸出物。若无法避免，则应首先采用较低的化合物特定阈值和质量标准，以充分控制其作为浸出物的含量。随后，应根据 ICH M7 指导原则评估制剂中高于适用 TTC 的所有浸出物是否具有致突变潜力。被认为具有潜在致突变性的浸出物应控制在 TTC 限度内；若已通过充分的致突变性研究排除了相关风险，则不受此限。

除致突变性评估外，还应对制剂中高于适用 QT 的所有浸出物进行一般毒性评估。如果有充分数据支持浸出物在患者最大潜在暴露下的安全性，则无需进行进一步毒理学评估（详细信息见附录 5）。相反，如果数据不足以支持浸出物的安全性，则需要采取措施将

潜在暴露降至已知可接受水平（材料更换等），或补充毒理学数据以佐证当前暴露水平的安全性，或进行风险/获益评估论证当前暴露水平的合理性。

需要注意的是，对于缺乏充分数据证明化合物安全性的浸出物，鼓励采用基于高度相似化合物（具有毒理学数据）的交叉参照法。若能识别出具有充分数据支持在观测水平下浸出物安全性的替代物，则无需进一步的安全性风险评估和/或研究。

如果认为需要生成新的毒理学数据，以支持浸出物暴露的安全性评估，在论证充分的前提下，可考虑采用新方法（NAM），包括计算机模拟模型和体外模型。否则，应考虑进行 ICH Q3A 和 Q3B 中描述的毒理学确认研究，以支持化合物的安全性评估。

6.4 给药途径相关注意事项和特殊情况（局部毒性问题）

潜在全身毒性的安全性风险评估通常足以支持浸出物暴露的安全性。然而，在某些情形中，由于化合物局部浓度可能导致脆弱组织损伤（例如肺部制剂、眼用制剂及脑内/鞘内/硬膜外制剂），潜在的局部毒性效应可能具有相关性。在相关情况下，毒理学风险评估应评估浸出物对局部组织毒性的潜在影响，以及可能降低减少此类影响的因素（如处方、辅料、接触时间和组织损伤恢复）。此外，当考虑潜在的局部毒性时，所使用的 SCT 应为致突变性阈值（即 TTC）、非致突变性阈值（即 QT）和局部毒性阈值（相关浓度转化为最高日暴露水平）中的最低者（按每日暴露量计算）。

6.4.1 眼用制剂

眼用产品通常为局部给药，而其中部分产品通过直接注射至眼部组织给药。目前缺乏数据来描述浸出物与眼部组织接触时的潜在局部毒性。基于历史先例，在缺乏相关数据库的情况下，对于最终待上市的眼用局部给药制剂中浓度超过 20 ppm 的浸出物，需完成化合物特定风险评估以论证其安全性。该浓度限度不适用于与眼部组织短暂接触的冲洗液。注射到眼部组织的产品未设定阈值，应对所有存在的浸出物进行定性安全性评估，即使其浓度低于 20ppm，该评估也可能具有相关性。

6.4.2 脑内、鞘内、硬膜外制剂

脑内、鞘内和硬膜外制剂可能直接与损伤后修复能力有限的重要中枢神经系统（CNS）组织相互作用，但目前缺乏充分数据来表征直接作用于神经组织或邻近区域的化合物的潜在毒性。*体外*数据表明，对于某些已知具有神经毒性的化合物，化学诱导的生物效应

可能在十亿分之一（ppb）的低浓度范围内发生。因此，化合物特定风险评估应考虑观察到的浸出物的局部浓度以及对神经组织（例如，神经元、星形胶质细胞、神经胶质细胞、髓鞘）的潜在局部毒性问题，包括对局部炎症反应可能性的评估。

6.4.3 经皮给药制剂

对于局部毒性效应，当浸出物为强效或极强效皮肤致敏物时，致敏潜力（见第 6.4.4 节）可能是最敏感的非遗传毒性终点。对于高效价化学品（HPC），皮肤致敏阈值（DST）推导为 1 μg/cm^2/天。经 ICH Q3D 中描述的经皮和透皮浓度限值（CTCL）计算进行转换后，该阈值对应于经皮给药制剂中 500 ppm 的浓度。因此，对于经皮给药制剂，可以使用与制剂中 500 ppm 浓度相对应的局部毒性阈值，低于该阈值时无需进行包括致敏潜力在内的局部非致突变毒性评估（见表 1）。

6.4.4 致敏潜力

致敏剂是反复暴露后可能引发超敏反应的化合物。对这些化合物的关注程度主要取决于三方面：该化合物的致敏潜力、暴露途径和暴露个体的易感性。已针对各种暴露途径描述了具有多种作用模式的不同类型的超敏反应，但目前仅经皮途径存在经验证的预测模型。本指导原则涉及诱发致敏潜力的风险，并提供了该风险的局部毒性阈值（如适用）。如果患者对某种化合物敏感，则可能在较低的阈值下引发致敏反应。

经皮暴露

大多数关于致敏潜力的数据来自于经皮给药途径。除人体数据外，还开发了*计算机模拟*、*化学分析*、*体外*和*体内*模型来表征化合物的皮肤致敏潜力。DST 是根据致敏效力得出的。[1,2]

如果经皮给予已知浸出物时，其浓度低于相应效力类别的 DST，则可以得出结论，预计不会产生皮肤致敏性，不需要采取进一步措施。如果超过 DST，则应评估关于致敏潜力的可用化合物特定数据。如果没有此类数据，或者当这些数据引起关注时，需要考虑风险缓解措施。措施可能包括更换浸出化合物的组件或降低浸出物水平。

由于透皮药物也经皮肤给药，因此可以使用相同的方法来评估其致敏潜力风险。对于多日贴剂，假设所有浸出物在一天内迁移，应使用数据证明较慢的迁移速率是合理的。

吸入暴露

目前关于化合物呼吸道致敏潜力的认知主要来自于人体数据。目前，尚未建立起适用于安全性风险评估的呼吸道致敏非临床模型。皮肤和呼吸道致敏剂的作用方式有共同点，但也存在差异，特别是在 T 细胞激活后。因此，皮肤致敏数据不应用于估计呼吸道致敏的风险，也不能提供呼吸道致敏的阈值。

呼吸道对具有致敏（和刺激）特性的化合物非常敏感[3]。因此，应评估任何可能具有致敏潜力或刺激性的结构元素的化合物（如异氰酸酯、腈、苯乙烯、短链醛）。如果认为一种化合物具有刺激性或致敏潜力，则应在评估该化合物的可用信息后，根据具体情况对患者风险进行评估。此外，应评估现有临床数据，以确定不良反应的证据。如果未发现刺激性或致敏性问题，则可以采用注射给药对应的全身毒性 QT 值，如表 1 所示。

注射暴露

关于致敏的潜在风险，应区分皮下/皮内给药途径与静脉/肌肉/腹膜内给药途径。在皮下给药途径中，药物在触发皮肤致敏的关键组织和细胞（即朗格汉斯细胞）附近进行给药。特别是当浸出物未能快速分布，且在皮下组织中滞留时间较长时，可能激活相同的作用机制。因此，在评估皮下给药浸出物的致敏潜力时，可参考皮肤致敏潜力的现有数据。同样，对于皮内给药制剂，皮肤致敏数据可能具有相关性。相比之下，应用于皮肤表面的化合物需要首先穿透皮肤屏障。考虑到这一差异，将皮下和皮内给药制剂的阈值设为比经皮给药制剂低 10 倍是合理的，即 50 ppm，而非 500 ppm。

在目前已知的全身性超敏反应（I-IV 型）中，每种类型都具有不同的作用模式。IV 型依赖于半抗原的形成，因此与皮肤致敏具有一些共同的机制。然而，与经皮给药相反，肌内和静脉给药的物质会在全身迅速分布，因此需要大量药物才能激活免疫系统并诱发致敏。由于浸出物在制剂中的浓度较低，因此一般认为通过静脉或肌内注射给药的药物不太可能引起致敏性问题。

6.5 ICH S9 产品的注意事项

对于 ICH S9 范围内的制剂，通常应根据上文第 3 节中概述的科学原则进行浸出物识别。可根据 ICH S9 中的“杂质评价”章节进行安全性风险评估。在此类情况下，TTC 将不再适用，SCT 将由 QT 定义。风险评估可重点关注目标患者人群的一般安全性，并参考 ICH S9 Q&A 2018，与 API 是否具有遗传毒性进行关联性考虑。

6.6 安全性评估内容

应对观察到的 1 类浸出物、检测水平高于相关 SCT 的 2 类浸出物以及浓度水平高于 1.0 mg/天的 3 类浸出物进行安全性评估。安全性评估应提供充分信息，以便就预期患者暴露水平的可接受性得出结论。附录 5 中详细描述了需要考虑的信息和得出可接受暴露水平的方法。

7. 术语表

分析评价阈值（AET）:
应对超过该阈值的可提取物或浸出物进行鉴别、定量，并报告进行安全性评估。

化学表征:
获取药品包装和药品生产组件等物品组成的化学信息的过程。

组件:
由一种或多种结构材料组成的单个物品，用于单一目的或执行单一和特定任务。

提取:
将受试物的成分转移到提取介质中的化学或物理过程。

关键质量属性:
一种物理、化学、生物或微生物属性或特性，应在适当的限度、范围或分布范围内以确保获得预期产品质量。

制剂:
在最终药品包装中用于上市的剂型。

原料药:
尚未进行配方的活性药品成分，随后可与辅料一起配方以生产剂型（或制剂）。

可提取物谱:
对提取研究中存在的可提取物的定性或半定量/定量说明。

浸出物谱:
对制剂中浸出物的定性和/或定量说明。

生命周期:
从最初的开发到上市，直到产品退市的产品生命中的所有阶段。

未见（不良）反应剂量（NO(A)EL）:

与对照组相比，在暴露人群中不会引起任何统计学或生物学上显著的不良反应的浸出物或可提取物的最高浓度或数量。

交叉参照：

一种通过使用来自其他结构相关物质的相同终点数据来预测一种物质的终点信息的技术。

安全边际：

特定浸出物的 PDE 与基于日剂量的实际患者摄入量之间的相关性。

结构材料：

用于构建包装或生产组件或系统的单个材料。

新药制剂：

药物制剂类型，例如片剂、胶囊、溶液、乳膏等，其尚未在某一区域或成员国注册，通常含有药物成分，并且可能含有辅料。

未观察到（有害）作用水平（NO(A)EL）：

与对照组相比，在暴露人群中不会引起任何统计学或生物学上显著的不良反应的浸出物或可提取物的最高浓度或数量。

每日允许暴露量（PDE）：

对于慢性暴露，药品中浸出物每天的最大可接受摄入量。

起始点（PoD）：

浸出物 PDE 计算的起点；可从人用剂量或适当的动物研究中得出。

界定限度（QT）：

当浸出物含量高于该阈值时，将被考虑用于非致突变毒性作用的安全性评估，除非其被认定为高度关注的浸出物。

安全性关注阈值（SCT）：

当浸出物含量等于或低于该阈值时，其致突变和非致突变毒性引发的安全性问题可忽略不计，除非该浸出物被认定为高度关注的浸出物。

模拟制剂：

对浸出倾向和浸出物溶解度而言，与制剂处方浸出特性非常相似的基质或溶剂。

物质（化合物、化学品、化学实体）：

不同元素或化学实体的组合，具有明确化学成分和特定的化学性质。

系统：

共同执行特定功能（如生产、给药或储存）的单个组件（或部件）的集合。

毒理学关注阈值（TTC）:

如 ICH M7 所述，当浸出物含量低于该阈值时，不考虑对其进行致突变效应安全性评估。

8. 参考文献

国际人用药品注册技术协调会（2006）。Q3A（R2）：新原料药中的杂质。

国际人用药品注册技术协调会（2006）。Q3B（R2）：新药制剂中的杂质。

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国际人用药品注册技术协调会（2022）。Q3D（R2）：元素杂质指导原则。

国际人用药品注册技术协调会（2023）。M7（R2）：评估和控制药物中 DNA 反应性（致突变）杂质以限制潜在的致癌风险。

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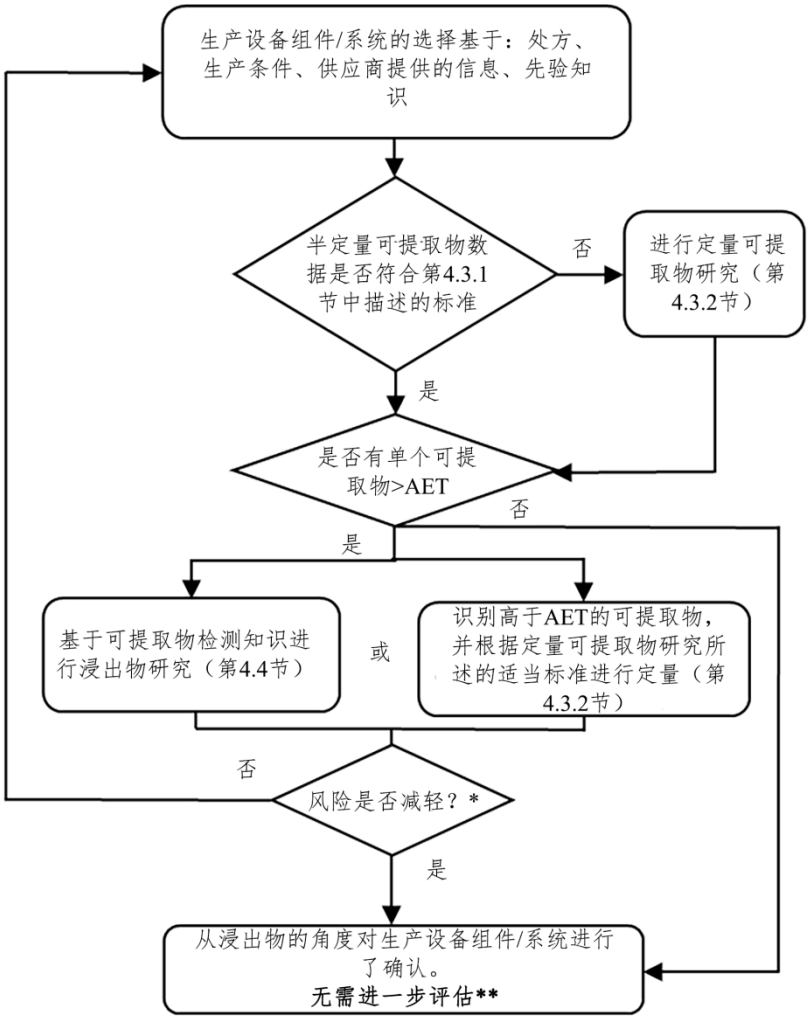
附录 1：E&L 风险评估和风险控制的典型工作流程

下图展示了生产组件/系统包装（图 4）以及包装和给药装置组件/系统（图 5）的组件确认中 E&L 整体风险评估和风险控制的典型工作流程。通常，对于生产组件/系统和大多数情况下的包装系统，应基于最差条件下的浸出物研究来进行安全性评估。然而，在某些低风险情形下，可以提出替代方法。在所有情形中，无论是类似于表 A.1.1 和表 A.1.2 中给出的示例，还是其他低风险情形，都应证明所采取的方法是合理的（见表 A.1.1 和表 A.1.2）。总体而言，数据要求的范围和后续的质量及安全性评估应与总体风险水平相匹配。

图 4：生产组件/系统的 E&L 评估相关风险识别和风险减轻的典型工作流程



有关方法确认和化学鉴别要求以及建议进行浸出物研究的情形，请参阅第 4.3 节。

*可提取物或浸出物的量低于各个化合物适用的安全性阈值。

**对于采用了相同或相似材料制造的多个组件的生产工艺，应评估最终制剂中的累积浸出物风险（见第 3.4.1 节）。

图 5：包装和给药装置组件 E&L 评估相关风险识别和风险减轻的典型工作流程

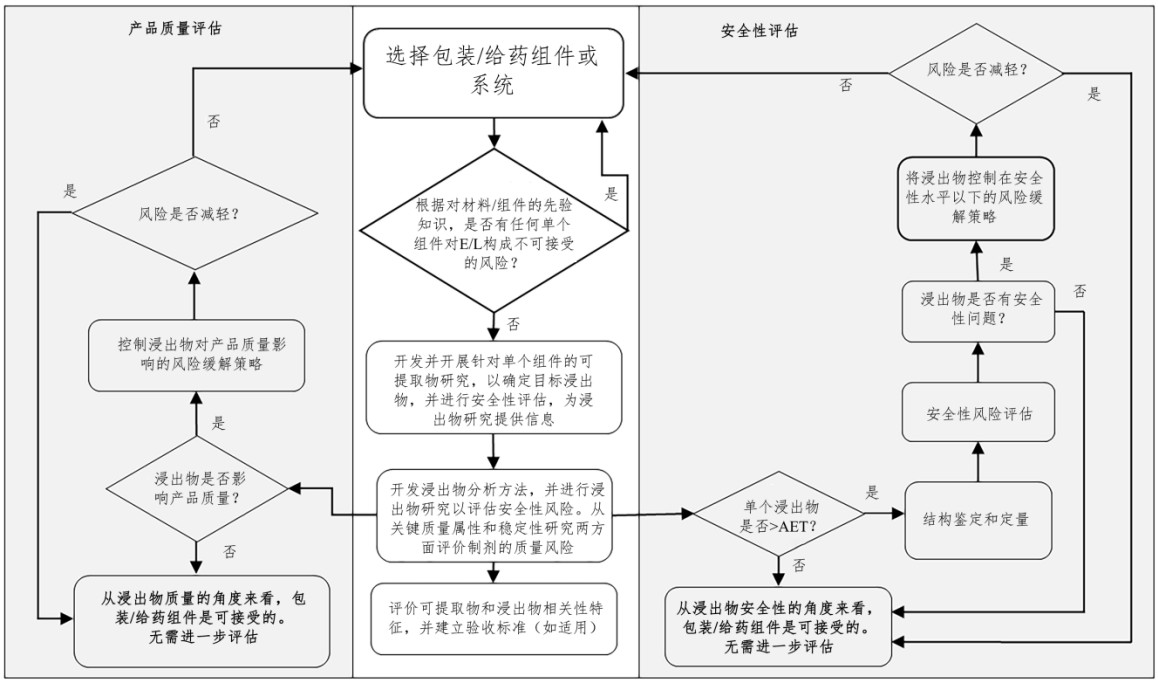


表 A.1.1：生产设备组件/系统风险情形

风险情形	潜在结果
情形1: 使用符合相关区域食品和/或药品级别要求的设备组件生产的固体口服制剂（见第3.2节）。	组件确认时无需额外进行可提取物或浸出物检测。
情形2: 使用符合相关区域食品接触安全法规的聚合物生产设备/系统生产的液体口服制剂，其材料使用符合相关规定，并且制剂的浸出倾向不大于相关规定中明确的浸出倾向（见第3.2节）。	组件确认时可能无需额外进行可提取物或浸出物检测。
情形3: 在半定量可提取物研究中，没有生产组件/系统的可提取物含量高于适用的AET（见第4.3.1节）。	
情形4: 在所有生产设备定量可提取物研究中检测、鉴别和定量的高于适用AET的可提取物均低于其适用的安全性阈值（TTC/QT或化合物特定AI/PDE）（见第4.3.2节）。	组件确认时可能无需额外进行可提取物或浸出物检测。

一般而言，应提供所有直接接触包装组件/系统和给药装置组件的全面可提取物和浸出物数据。然而，对于整体风险较低的情形（见第 3.2 节图 2），经过充分论证合理的前提下，可能只需提供定量可提取物研究的简化数据包。请参见第 3.4 节阐明的应进行浸出物研究以解决具体问题并证明组件可接受性的情形。

表 A.1.2: 包装和给药装置组件的简化数据包示例

示例*	潜在结果
示例 1: 口服制剂的包装系统组件符合区域食品接触法规，包括其中规定的配方、生产、质量标准、检测结果和使用限制（见第 3.2 节）。	组件确认时可能无需额外进行可提取物或浸出物检测。
示例 2: 储存在良好表征的包装系统中的冷冻、非冻干制剂（即，根据申请人提供的先验知识）。制剂在短时间内解冻并给药，且从灌装开始到冷冻的持续时间很短（例如，<24 小时）（见第 3.4.1 节）。	组件也许能够通过使用适当溶剂且持续时间充分延长的定量提取物研究进行确认。
示例 3: 与口服制剂短时/一过性接触的给药装置组件(如口服注射器、口服量杯)符合区域食品接触法规。	组件确认时无需额外进行可提取物或浸出物检测。

表 A.1.1 和表 A.1.2 的注 1:

有关可提取物与浸出物研究的建议，请参见第 4.3 节（如适用）。

有关适当文件和合规性的建议，请参见第 3.5 节（如适用）。

*如果未检测到高于 AET 的可提取物，或仅检测到少量高于 AET 且低于其适用的安全性阈值的可提取物（如 3 类浸出物；参见第 6 节），结合先验知识，经充分论证合理后可使用简化数据包。当申请提交简化数据包时，建议与相关区域监管机构/卫生监管部门沟通，以确认所用方法可被接受。

附录 2：研究类型

表 A.2.1：可提取物、浸出物和模拟浸出物研究总结

研究类型	总结
可提取物	**实验条件：** 采用相对激进的条件，结合与制剂处方在最差条件下的预期浸出倾向相关的溶剂和提取条件，以提取比实际使用条件下产生更多数量或更高含量的化学实体，而不导致所提取化学实体或材料发生化学变化。通常会使用一系列对制剂处方具有代表性的溶剂。 **目的：** 进行材料/组件的表征，并为危害评估提供合适的数据，以指导组件的选择。在某些低风险情形中（见附录 1），可利用可提取物的质量风险评估进行材料/组件的确认。 产生在数量和含量上远超实际浸出物的化学实体（潜在浸出物）。 评估在预期使用条件下可能实际浸出的化学实体。 识别潜在浸出物，以便进行危害评估和安全性风险评估（如适用）。
浸出物	**实验条件：** 在有效期和使用中稳定性期间检测待上市制剂。可补充加速稳定性放置条件下的制剂检测数据（如相关）。 **目的：** 在有效期和使用期间定量测定并监测目标浸出物。 对高于 AET 的非预期（非目标）浸出物进行鉴别和表征。 在有效期和使用期间观察到的浸出物能够进行毒理学风险评估。
模拟浸出物	**实验条件：** 在模拟生产和/或长期放置条件下（pH 值、温度、持续时间），使用模拟制剂对生产组件和/或待上市制剂包装系统进行检测。可补充加速稳定性条件下的数据（如相关）。 **目的：** 在长期放置和使用期间定量测定并监测目标浸出物。 对高于 AET 的非预期（非目标）浸出物进行鉴别和表征。 在极少数情况下，如充分论证合理，且经区域监管部门确认并同意，可用于代替浸出物研究进行毒理学风险评估。

有关可提取物与浸出物研究的详细建议，请参见第 4.3 节（如适用）。

附录 3：AET 计算

所提供的每个示例均基于所用制剂适用的 SCT（μg/天）。在某些情况下，替代起始点可能相关（例如对于潜在的 1 类浸出物）。在所有计算过程中均应假设最差条件，例如制剂的最大批准剂量。提供了可提取物和浸出物研究的常见示例。AET 的计算应清晰标明单位及计算方法。无论用于表示 AET 的单位如何，给定研究的最终值须换算至与患者暴露量相同的水平（即 SCT 乘以分析不确定因子[UF]）。

最大日剂量（MDD）和安全性关注阈值（SCT）

对于每种产品，AET 的计算应基于 MDD。MDD 是药物在一天内给药的最大批准剂量。为确定 SCT，应考虑 TTC 与 QT，如表 1 所示。SCT 基于其中的最低值确定。

间歇给药

如果不是每天给药，则应遵循 ICH M7 来推导适用的 TTC（例如，当总给药天数≤30 天时，TTC = 120 μg）。

在 QT 推导中，当总给药天数≤30 天或给药频率为每月一次或更少时，可使用≤1 个月的 QT。

多日产品

对于使用后可能在患处保持多天的产品（例如，多日贴剂、长效注射剂、植入物），适用的 TTC 由治疗的总持续时间决定。对于致突变杂质，根据 ICH M7，应使用平均每日暴露量计算。对于非致突变浸出物，默认假设所有浸出物在一天内迁移。此时，适用的 QT 由总给药次数定义。迁移速率较慢会减少非致突变浸出物的日剂量，但会增加给药天数。如采用较慢的迁移速率，则应使用数据证明其是合理的。

AET 计算示例

可提取物情形 1：液体制剂生产工艺中使用的过滤器

(1) AET（μg/过滤器）= SCT（μg/天） × *UF* × 每批制剂的剂量单位数* ÷ 每批过滤器数

(2) AET（μg/g 过滤器）= AET（μg/过滤器）÷ 重量（g）/过滤器

(3) AET（μg/mL 提取溶剂）=AET（μg/过滤器）÷ 提取溶剂（mL）/过滤器

(4) AET（μg/cm^2）=AET（μg/过滤器）÷ 接触表面积（cm^2）/过滤器

*应使用单日给药的 MDD 和最小潜在批量来确定每批制剂的剂量单位数(即最差条件)。因此，如果单日内给予的最大批准剂量为 100 mg（= 0.1 g），最小潜在批量为 1 kg（= 1000 g），则每批制剂的剂量单位数为 1000 g/批 ÷ 0.1 g/剂 = 10000 剂/批。

可提取物情形 2：液体制剂包装系统（CCS）中使用的橡胶瓶塞

(1) AET（μg/胶塞） = SCT（μg/天） × *UF* × 体积/瓶（mL/胶塞） ÷ 日最大剂量（mL）*

(2) AET（μg/g 胶塞） =AET（μg/胶塞） ÷ 胶塞重量（g）

(3) AET（μg/mL 提取溶剂） =AET（μg/胶塞） ÷ 提取溶剂（mL）/胶塞

(4) AET（μg/mL 提取溶剂） =AET（μg/g 胶塞） ÷ 提取溶剂（mL）/胶塞克数

*应使用单日内给予的最大批准体积剂量（即最差条件）。如果剂量以质量（例如，mg/天）为基础进行描述，则应根据活性成分的浓度将其转换为体积（mL）。因此，如果单日内给予的最大批准剂量为 100 mg（= 0.1 g），制剂浓度为 10 mg/mL，则计算的日最大剂量为 100 mg ÷ 10 mg/mL = 10 mL。

浸出物情形 1：液体制剂生产设备的浸出物

(1) AET（μg/批）= SCT（μg/天）× *UF* ×每批制剂的剂量单位数*

(2) AET（μg/mL 制剂）= SCT（μg/天）× *UF* ÷ 日最大剂量（mL）

*应使用单日给药的 MDD 和最小潜在批量来确定每批制剂的剂量单位数(即最差条件)。因此，如果单日内给予的最大批准剂量为 5 mL，最小潜在批量为 10 L（= 10000 mL），则每批制剂的剂量单位数为 10000 mL/批 ÷ 5 mL/剂 = 2000 剂/批。

浸出物情形 2：预灌封注射器（PFS）的浸出物

(1) AET（μg/mL 制剂）= SCT（μg/天）× UF ÷ 日最大剂量（mL）*

(2) AET（μg/PFS）=AET（μg/mL 制剂）×每支 PFS 的体积（mL）

*应使用单日内给予的最大批准体积剂量（即最差条件）。如果剂量以质量（例如，mg/天）为基础进行描述，则应根据活性成分的浓度将其转换为体积（mL）。因此，如果单日内给予的最大批准剂量为 10 mg，制剂浓度为 10 mg/mL，则计算的日最大剂量为 10 mg ÷ 10 mg/mL = 1 mL。

附录 4: 浸出物的效力分类

潜在浸出化合物的化学性质各不相同，其安全性数据库也是如此。为了在保护患者的同时能有效设定安全性阈值，除指导原则中应用的阈值外，还开发了浸出物分类办法。分类办法基于全身效应，广泛适用于所有给药途径。然而，适用于特定给药途径制剂的浓度阈值（如第 6.1 节表 1 所示）不受该分类办法的影响。因此，无论浸出物类别如何，浸出物潜在局部效应的默认浓度阈值相同。

1 类浸出物一般是指在该类化合物的使用场景中，本指导原则中所述的致突变和全身效应阈值尚未被证明足以保护患者安全。因此，对于 1 类浸出物，可接受暴露水平应基于特定化合物来确定。1 类浸出物包括: ICH M7 关注队列化合物、AI<1.5 μg/天的 ICH M7 1 类化合物，以及按照附录 5 所述方法推导每日允许暴露量（PDE）的非致突变浸出物，其设定的 QT 值可能不足以保护患者安全（见附录 6）。

2 类是默认的浸出物分类，对于本指导原则中描述的慢性注射给药致突变性（TTC）和全身毒性（QT）阈值，该分类包含的化合物被视为对患者足够安全。这包括本指导原则中未明确列出 PDE 的所有化合物。

3 类浸出物是指全身毒性效力相对较低的化合物，其衍生的慢性注射 PDE 超过典型浸出物水平。若每日暴露水平低于 1.0 mg/天时观察到 3 类浸出物，则无需进行进一步安全性确认。

上述浸出物类别的汇总见下表 A.4.1。高于表 A.4.1 中确定的浸出物水平应按照附录 5 所述进行科学论证。

647 **表 A.4.1: 浸出物的效力分类**

1 类 - 应避免的浸出物 致突变物/预测的致突变物 属于 ICH M7 关注队列的浸出物（黄曲霉毒素类、N-亚硝基和烷基偶氮氧化合物）。 浸出物符合 ICH M7 1 类杂质标准，且 AI<1.5 µg/天。 非致突变物/预测的非突致变物 具有推导得出的注射给药 PDE 的浸出物，其既定的 QT 值可能不足以保护患者安全（见下表）。 *在实际可行的情况下，应避免使用 ICH Q3E 1 类浸出物，其暴露量不应超过有科学依据的化合物特定可接受暴露水平。*
2 类 - 需限制的浸出物 致突变物/预测的致突变物 浸出物符合 ICH M7 1 类杂质标准，且 AI≥1.5 µg/天。 符合 ICH M7 2 类或 3 类杂质标准的浸出物。 *ICH Q3E 2 类致突变（或预测致突变）浸出物不应超过: (1) TTC 或短于生命周期的 TTC（如适用），或(2) 制剂相关 QT。* 非致突变物/预测的非突致变物 经附录 5 所述方法确定，注射给药 PDE> QT 的浸出物（不包括 3 类浸出物）。 *ICH Q3E 2 类非致突变（或预测非致突变）浸出物在不超过制剂相关 QT 值时即视为合格，无需进一步安全性论证。*
3 类 - 潜在毒性相对较低的浸出物 非致突变浸出物的慢性注射给药 PDE 超过典型观察到的浸出物水平。 *ICH Q3E 3 类浸出物在不超过 1.0 mg/天或化合物特定 PDE（见下表和支持文件）的情况下即视为合格，无需进一步安全性论证。*

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649 **1 类 - 应避免的浸出物**

化合物	CAS#	急性可接受暴露水平（µg/天）		慢性 PDE（µg/天）		相关材料
		口服	注射	口服	注射	
苯并(a)芘	50-32-8	13	1.3	2.6	0.26	炭黑
双酚 A	80-05-7	2083	21	417	4	聚碳酸酯和环氧树脂

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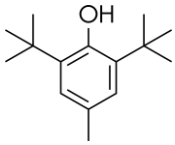
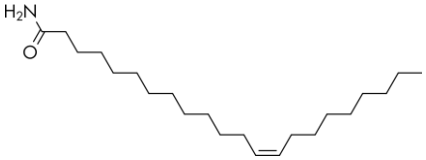
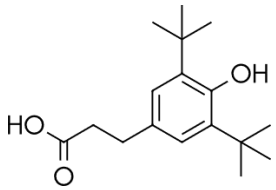
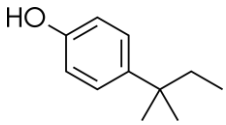
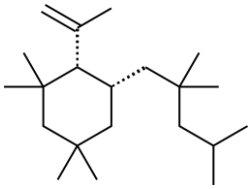
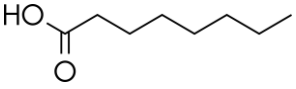
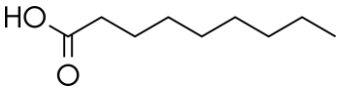
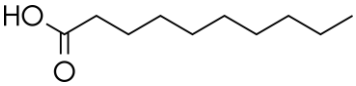
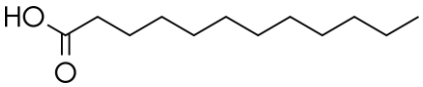
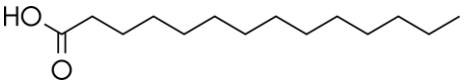
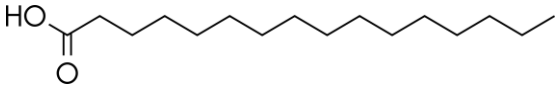
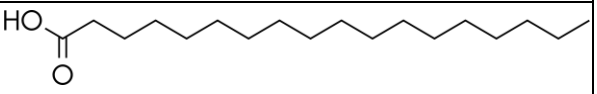
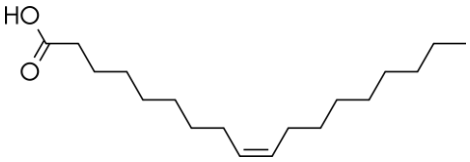
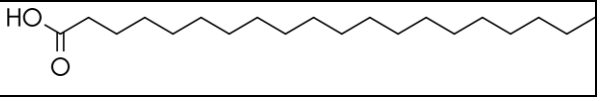
651 **3 类 - 潜在毒性相对较低的浸出物（慢性 PDE ≥ 1 mg/天）。专论见支持文件。**

化合物	CAS#	化学结构
BHT	128-37-0	
芥酸酰胺	112-84-5	
3-(3,5-二叔丁基-4-羟基苯基)丙酸	20170-32-5	
4-叔戊基苯酚	80-46-6	
橡胶低聚物 $C_{21}H_{40}$	114123-73-8	
脂肪酸		
辛酸（C8）	124-07-5	

壬酸（C9）	112-05-0	
癸酸（C10）	334-48-5	
月桂酸（C12）	57-10-3	
肉豆蔻酸（C14）	544-63-8	
棕榈酸（C16）	57-10-3	
硬脂酸（C18）	57-11-4	
油酸（C18）	112-80-1	
二十二酸（C22）	112-85-6	

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附录 5: 确定暴露限度的方法

背景

对于超过本指导原则中定义的适用安全性阈值的 1 类和 2/3 类浸出物，需要进行进一步的安全性评估，以确定当患者接受特定制剂给药时与这些浸出物相关的潜在暴露风险。对于绝大多数潜在浸出物，目前尚未确定用于支持任何制剂中化合物安全暴露的每日允许暴露量（PDE）。此外，由于现有制剂的性质不同，以及可提取物和浸出物安全性风险评估的复杂性，通用方法（如既定的 PDE）并不总是最合适的。虽然本指导原则的重点不是设定单个化合物的可接受暴露水平，但通常可能需要在逐个产品的基础上确定特定化合物的限度。因此，本附录通过基于风险的方法，为在各种制剂类型和给药场景下适当地评估浸出物安全性提供了指导。

在判定浸出物潜在患者暴露水平可接受性的过程中，不同制剂和场景间对信息充分程度的要求可能变化甚大，且可能使用多种方法来确定其可接受性。最直接的方法是采用已建立的安全暴露水平，这些暴露水平已保守地假设了最差条件。因此，当现有 ICH 指导原则（例如 Q3C 或 M7）中有既定的 PDE 时，在满足所有必要考量因素的情况下，引用该值即可。而另一种可能更为适用的方法是，使用类似方法和科学原则（如之前在指导原则中确定的）得出的可接受暴露水平。在其他情形下，定义明确、支持充分且论证合理的 NOAEL 与预期患者暴露量之间的剂量比可能极大（例如>10000），因此无需详细推导。

尽管在某些情况下，体外和/或体内研究（作为最后手段）可能被认为是确定可接受暴露水平所必需的，但鼓励通过可用计算机模拟分析，并对类似化合物（即替代化合物）进行交叉参照来提供科学论证（如适用），以确定可接受暴露水平。

尽管有多种计算机模拟毒理学工具可用，但在本指南的框架下，致突变性是唯一的毒理学终点。恰当开展的致突变性试验目前已被确认可独立用于替代生物学数据（参见 ICH M7）。然而，在有适当的科学依据的情况下，应将使用计算机模拟、体外、或体内模型对其他毒理学终点的预测纳入安全性风险评估中，以基于证据权重的风险评估方法补充现有数据。在每个类别中，应优先使用那些考虑到相关暴露途径的已验证模型的数据。

由于大量潜在浸出物的毒理学数据集有限甚至缺乏，也可考虑采用交叉参照法。在交叉参照法中，替代化合物（或多种替代物）的相关毒理学数据将作为证据权重法的一部分，或在无数据时作为目标浸出物数据的替代，用于支持目标浸出物的安全性评估。若安全性评估涉及替代化合物，应提供明确的替代物选择理由。在选择合适的替代物时，应考虑各种属性（如已知），包括作用方式、主要毒性基团和周围的化学环境（例如，存在可能影响生物活性的官能团）、总体结构相似性、毒代动力学性质、理化性质（例如，极性、溶解度、电离性以及分子量）。在有充分理由的情况下，可使用新方法学（NAMs）的计算机模拟工具和数据支持替代物的选择，并为交叉参照方法提供信息，但需要考虑上述标准。对于替代物如何纳入相关浸出物的安全性评估应进行科学论证。还应指出并适当说明与交叉参照方法相关的潜在不确定性，例如在用于确定可接受暴露水平时（见下文 F7）。

待评价并纳入安全性评估的数据

为了确立特定制剂中浸出物的安全性，需提供对化合物的全面安全性评估。下面列出了要包括的数据元素（如数据可用）。还应评估这些数据集的相关性和质量。如上所述，替代化合物数据与计算机模拟分析的使用也应纳入安全性评估并证明其合理性。此外，如将观察到的多个浸出物分组评价，则须包含该分组的详情与依据。

药理学/生物学数据

- 考虑可能影响总体安全性评估的潜在生物学效应（例如内分泌干扰、抗胆碱能活性）的体内或体外数据。

毒代动力学（TK）

- 评估和总结与制剂给药途径相关的数据
- 考虑吸收和生物利用度之间的潜在差异，尤其是当需要进行途径间外推时。
- 应考虑生物累积潜力。

全身毒性

- 总结相关的急性、亚急性/亚慢性和慢性毒性研究。
- 指出数据与人类的相关性。
- 识别评估人体全身毒性潜力的关键研究。

致敏潜力/局部刺激性

- 应总结相关可用的临床和非临床数据（如有理由，可补充计算机模拟评估）。

- 监管分类（或缺乏监管分类）可酌情加以利用。

生殖与发育毒性（DART）

- 除了总结现有的 DART 研究外，还应评估和纳入关于内分泌干扰特性的数据和/或分类。

遗传毒性和致癌性

- 总结现有数据，并指出与人类的潜在相关性。
- 如果数据不可用，可使用符合 ICH M7 的计算机模拟方法进行评估（注：ICH M7 4 类不适用于浸出物）。
- 如适用，应提供遗传毒性和/或致癌性的机制，因为这与可接受暴露水平的确定高度相关。

附加信息

- 还应包括安全性评估的其他相关信息（如有）。
- 示例：现有基于健康的风险限度/评估、临床和流行病学数据、类似/相关化合物的毒理学数据

可接受暴露水平的计算

除可接受摄入量（AI）等其他基于健康的限度外，PDE 概念在 ICH 指导原则中已被作为基于健康的暴露限度予以落实，其计算过程在各指导原则间基本一致。这种相同的基本方法已用于生成 PDE 值，以支持当前指导原则中确定的界定限度（包括生物利用度和使用交叉参照法时的额外校正因子）。下文简要描述并总结了该方法，其可用作特定制剂中浸出物可接受暴露水平的基础。

虽然此处描述的推导可接受暴露水平的方法基于其他 ICH 指导原则中的 PDE 方法，但需指出，可接受暴露水平不一定等同于 PDE。根据定义，PDE 为终生暴露水平，适用于多种产品，而特定产品的可接受暴露水平则需考虑暴露持续时间和最大日剂量。在对上述浸出物的可用数据与信息进行回顾和评价后，开始推导过程：首先选择合适的起始点（PoD），随后应用校正因子（F1-F7）。应使用最相关的研究来选择 PoD，同时考虑使用的物种、暴露途径、持续时间、监测的毒理学终点以及研究数据的质量；如有充分理由，可不选择最低 NO(A)EL 作为 PoD。以往的指导原则使用了特定的校正因子，用于描述种间和种内变异性（分别为 F1 和 F2）、采用 PoD 的研究持续时间（F3）、毒性严重程度

（F4）以及说明 NOAEL 缺失的因子（F5）。由于浸出物涵盖广泛的化学空间，不同给药途径的生物利用度可能有所差异。由于毒性数据通常仅适用于单一给药途径，故本指导原则建议纳入一个额外的校正因子（F6），以考虑在进行给药途径间外推时生物利用度的差异。此外，如前所述，有时可能需要使用替代化合物的 PoD（交叉参照法）。因此，建议使用另一个校正因子（F7）来解释与使用该替代化合物相关的不确定性。

由于 F1-F5 值的选择标准已在现有指导原则中详细说明，故在此不再赘述。新引入的与浸出物相关的校正因子（F6 和 F7）总结如下。

F6 = 用于考虑暴露途径外推的可变因子（例如，口服给药至注射给药）。

在缺乏足够的通过制剂预期暴露途径获得的浸出物毒性数据的情况下，应使用 F6 来调整 PoD 研究给药途径与制剂暴露途径之间生物利用度的相关差异。理论上，F6 的取值应基于母体化合物的生物利用度数据。若采用放射性标记研究，应将其表述为吸收作用，因无法明确放射性标记物是母体化合物、代谢物，或是两者的混合物。如果数据质量良好，相对生物利用度估计值可直接用于确定 F6 的值。当生物利用度估计值存在显著不确定性时，可替代应用默认因子。例如，当使用口服毒性数据推导注射给药的可接受暴露水平时:

口服生物利用度<1%时，F6 = 100（除以校正因子 100）

口服生物利用度≥1%且<50%时，F6 = 10（除以校正因子 10）

口服生物利用度≥50%且<90%时，F6 = 2（除以校正因子 2）

口服生物利用度≥90%时，F6 = 1（除以校正因子 1）

在缺乏足够体内数据的情况下，应采用其他方法作为证据权重策略的一部分或代替*体内*数据。例如，如果有适当的支持和科学依据，可以使用 NAM（结合估计吸收和内部清除率的体外数据以及计算机模拟 PBPK 模型）来生成数据以评估生物利用度。或者，建议 F6 的默认校正因子为 100。如需采用不足 100 的校正因子，需提供理由（例如，基于化合物的理化特性进行推理）。当可获得替代分子药物的适当生物利用度数据并允许采用交叉参照方法时，若有充分依据，可利用这些数据为生物利用度估计提供信息。

对于某些给药途径，如吸入给药，在确定合适的 F6 值时，需要额外考量。例如，对于吸入毒理学研究，呼吸道沉积、呼吸吸收率和肺部代谢的数据为 F6 的确定提供参考。对于经皮给药途径，若毒代动力学数据可用，则可用于估计全身剂量。在评估浸出物的

估计每日总全身剂量时，可参考注射给药 QT。在缺乏毒代动力学数据的情况下，当从皮肤剂量外推至全身剂量时，应采用较为保守的吸收率设定，即对多数有机溶剂稀释液默认采用 70%吸收率，对水基或分散类稀释液默认采用 50%吸收率。如果分子量大于 500 且 logPow 低于-1 或高于 4，则假定默认吸收因子为 10%。当存在于旨在增强经皮吸收的经皮给药制剂中，或皮肤完整性可能受损时，浸出物可更深程度地渗透皮肤。在此类情况下，应假定更高的吸收率。

F7 是仅在采用交叉参照方法时适用的可变因子。

当使用交叉参照策略时，根据与目标浸出化合物的相似性或非相似性水平，可使用高达 5 的因子。通常情况下，若替代物符合本指导原则所述相似性标准，F7 可设定为 1。

参考文献

应提供支持拟定 PDE 的参考文献（或其他文件）的副本。

安全边际（MOS）和浸出物水平高于计算的可接受暴露水平或既定 PDE 的理由

对于已确定可接受暴露水平（如 PDE 或 AI）的物质，可以使用以下公式计算安全边际:

$$\text{安全边际} = \frac{\text{可接受暴露水平}}{\text{潜在患者暴露}}$$

对于任何安全边际（MOS）小于 1 的物质，应考虑采取可能减少或消除相关浸出物的风险缓解措施（如选择替代材料）。或者，应证明大于可接受暴露水平（如 PDE）的限度不会对特定制剂造成安全性问题。在某些情况下，考虑到相关产品特定的考虑因素，可以接受高于计算或确定的 PDE 的浸出物可接受暴露水平。包括但不限于以下情形:

- 患者接受间歇给药;
- 短期给药（即 30 天或更短）;
- 患者人群有限（例如，仅限成年男性）;
- 特定适应症（例如，危及生命、未满足的医疗需求、罕见疾病）。

此外需注意，对于非终生给药的药物，当选择短期暴露毒性研究作为 PoD 时，可以考虑使用较低的 F3 值。此时，推导出的是可接受暴露水平，而非 PDE。若存在其他更长期的动物研究，这些研究可能根据与短期暴露无关的发现得出 NOAEL 值，因此可能不是特定制剂最合适的 PoD 值。虽然在此类情况下，可以接受短期暴露的毒性研究作为 PoD，但这不包括 LD_{50} 研究。

790 在产品间歇给药的情况下，如果有数据支持，可以应用 ICH Q3D 中描述的 F2 子因子
791 法。或者，可以修改 F3 的值。

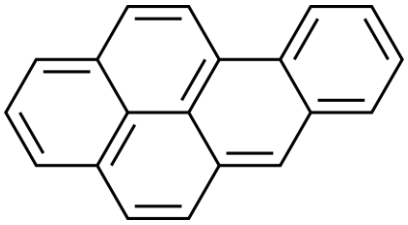
792 **表 A.5.1：确认浸出物时证据权重的论证考虑因素示例。如可能，应优先考虑非动物方**
793 **法。**

毒理学终点	**非动物方法（有依据）**	***体内*模型**
一般全身毒性	交叉参照	ICH Q3A 和 Q3B 中描述的确认研究区域指导原则（如 USP）
局部毒性	交叉参照 *体外*模型：细胞毒性（USP <87>, <1031>） 牛角膜混浊（BCOP：OECD 437）	应考虑进行 ICH Q3A 和 Q3B 中描述的毒理学确认研究 根据其他标准（如 ISO 10993）评估的局部耐受性
遗传毒性	*计算机模拟*模型（根据 ICH M7）	参照 ICH M7

794

附录 6: 1 类浸出物专论

苯并[a]芘



苯并[a]芘（CAS 号 50-32-8）的急性可接受暴露水平和慢性 PDE 值汇总

苯并[a]芘		
给药途径	**口服给药（µg/天）**	**注射给药（µg/天）**
急性可接受暴露水平*	13	1.3
慢性 PDE	2.6	0.26

*急性可接受暴露水平适用于≤1 个月的每日给药

前言

苯并[a]芘（BaP）是一种由五个稠合苯环组成的多环芳烃（PAH）。它不是商业上生产或使用的，而是由于有机物质的不完全燃烧而形成的。BaP 可能会从含有炭黑的材料中浸出。

BaP 是一种致突变致癌物，因此，除以下得出的相关可接受暴露水平或 PDE 值外，还应根据现行版 ICH M7 指导原则对其进行控制。基于非致突变终点，在 ICH Q3E 中确定了两个口服给药和两个注射给药的 BaP 值。

安全性总结和限制性非致突变毒性

在重复给药毒性研究（包括成年和幼龄动物）中，经口接触 BaP 已被证明会导致发育毒性（包括发育神经毒性）、生殖毒性和免疫毒性。总体而言，人体研究报告的毒理学效应通常类似于在动物中观察到的效应，并为与 BaP 暴露相关的危害提供了定性的支持性证据。

基于 BaP 的关键非致突变作用，选择新生大鼠的非 GLP 经口给药发育毒性研究（Chen 等人，2012 年）作为推导口服和注射给药 PDE 的 PoD 研究。

口服可接受暴露水平和 PDE

Chen 等人于 2012 年进行的大鼠神经发育研究中，新生大鼠在出生后第 5 至 11 天经口灌胃给予 0、0.02 mg/kg、0.2 mg/kg 和 2 mg/kg 剂量的 BaP。鉴于各组/研究间观察结果的一致性（即，这些反应在两个独立大鼠队列中均受影响，包括幼年和成年大鼠测试；且多项研究中观察了相似的影响）和反应的敏感性，以及剂量组间观察到的剂量-反应关系，因此选择三种行为试验（Morris 水迷宫、高架十字迷宫和旷场试验）中的改变反应作为异常行为的关键影响判定依据。对三个终点进行基准剂量（BMD）建模得出的 BMDL1SD 值范围为 0.092 - 0.16 mg/kg·天。取该范围的下限，即 0.092 mg/kg·天，作为神经发育研究中的 PoD。

口服给药计算	
PoD	**0.092 mg/kg/天**
BW	**50 kg**
F1（幼鼠）	**7**
F2（种内变异性）	**10**
F3（PoD 研究持续时间：出生后第 5 至 11 天）	**急性可接受暴露水平为 1**
	慢性 PDE 为 5； PoD 研究未涵盖的大脑发育关键时期。
F4（行为影响）	**5**
F5 (BMDL1SD)	**1**
F6（PoD 途径外推）	**不适用**
急性可接受暴露水平 = 0.092 mg/kg/天 x 50 kg / (7 x 10 x 1 x 5 x 1) = 0.013 mg x 1000 µg/mg = 13 µg/天	
慢性 PDE = 0.092 mg/kg/天 x 50 kg / (7 x 10 x 5 x 5 x 1) = 0.0026 mg x 1000 µg/mg = 2.6 µg/天	

注射可接受暴露水平和 PDE

在缺乏注射重复给药毒性研究数据的情况下，基于 BaP 的理化特性（MW＝252.3 g/mol，预测 LogP 3.0（PubChem，2024）），采用相同 PoD 研究的数据推导包含生物利用度校正因子（F6）的注射给药 PDE。

注射给药计算	
PoD	**0.092 mg/kg/天**
BW	**50 kg**
F1（幼鼠）	**7**
F2（种内变异性）	**10**
F3（PoD 研究持续时间：出生后第 5 至 11 天）	**急性可接受暴露水平为 1**
	慢性 PDE 为 5；PoD 研究未涵盖的大脑发育关键时期。
F4（胎儿行为影响）	**5**
F5 (BMDL)	**1**
F6（理化特性）	**10**
急性可接受暴露水平 = 0.092 mg/kg/天 x 50 kg / (7 x 10 x 1 x 5 x 1 x 10) = 0.0013 mg x 1000 µg/mg = 1.3 µg/天	
慢性 PDE = 0.092 mg/kg/天 x 50 kg / (7 x 10 x 5 x 5 x 1 x 10) = 0.00026 mg x 1000 µg/mg = 0.26 µg/天	

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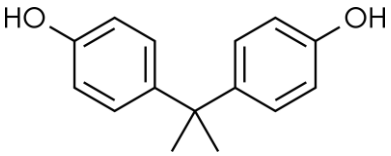
PubChem（2024）CID 2336 化合物摘要：苯并[a]芘，美国国家生物技术信息中心。检索日期：2024 年 05 月 02 日，来源：https://pubchem.ncbi.nlm.nih.gov/compound/Benzo_a_pyrene

Chen, C; Tang, Y; Jiang, X; Qi, Y; Cheng, S; Qiu, C; et al. (2012). Early postnatal benzo(a)pyrene exposure in Sprague-Dawley rats causes persistent neurobehavioral impairments that emerge postnatally and continue into adolescence and adulthood. Toxicol Sci 125: 248-261. https://academic.oup.com/toxsci/article/125/1/248/1668305.

双酚 A



双酚 A（CAS 号 80-05-7）的急性可接受暴露水平和慢性 PDE 汇总

双酚 A		
给药途径	**口服给药（µg/天）**	**注射给药（µg/天）**
急性可接受暴露水平*	**2,100**	**21**
慢性 PDE	**420**	**4.2**

*急性可接受暴露水平适用于≤1 个月的每日给药

前言

双酚 A（BPA）是 4,4'-甲烷二基二苯酚，其中亚甲基氢被两个甲基取代。它是聚碳酸酯塑料的关键组成部分，也是制造环氧树脂单体的前身。BPA 可能存在于药品生产过程中使用的内包装材料和生产设备、药品容器、药品/器械组合以及肠外营养袋中（Parris 等人，2020 年）。

安全性总结及限制性毒性

BPA 无致突变性和遗传毒性。ECHA 列出的 BPA 能够对人体产生皮肤致敏反应，并可能损害生育能力或危害胎儿。BPA 对皮肤无刺激性；但对眼睛有刺激性（ECHA，2024 年）。欧洲药品管理局（EMA）要求使用关键终点，以最大限度地降低与人类健康风险评估相关的不确定性；由于 ICH Q3E 与 EMA 标准保持一致，因此针对 BPA 作为药品潜在可提取物/浸出物的评估，采用了非致突变 PDE 的推导方法（EFSA EMA，2023 年）。

口服可接受暴露水平和 PDE

在小鼠的两代研究中测试了 BPA（Tyl 等人，2008 年）。该研究符合 GLP 和 OECD 416 标准，在小鼠中评估了饮食中 BPA 浓度分别为 0、0.018、0.18、1.8、30、300 或 3500 ppm（约 0.003、0.03、0.3、5、50 或 600 mg/kg/天）时的影响。研究采用了自由采食方式。同时设立了饮食中含 17β-雌二醇的同时期阳性对照组（0.5 ppm；雌雄各 28 只），以评估内分泌干扰潜力。

F0 代动物在交配前 8 周（即直至约 14 周龄）期间被给予相应配方饲料。随后，动物进入交配期，持续 14 天。动物在妊娠期（约 20 天）和哺乳期（3 周）期间继续接受给药。

在任何剂量水平下，均未观察到 BPA 对成年动物交配、生育能力、妊娠指标、卵巢原始卵泡计数、发情周期、交配前间隔、子代性别比、出生后存活率、精子参数以及生殖器官重量和组织病理学（包括睾丸和前列腺）的相关影响。在成年动物中观察到的全身效应包括：浓度≥300 ppm 时的小叶中心肝细胞肥大、体重减轻、肾脏和肝脏重量增加、小叶中心肝细胞肥大以及雄性动物发生肾性肾病。综上，生殖毒性的 NOAEL 为 300 ppm（约 50 mg/kg/天），成年动物（F0）全身毒性的 NOEL 为 30 ppm（约 5 mg/kg/天）。

口服计算	
PoD	**5 mg/kg/天**
BW	**50 kg**
F1（小鼠）	**12**
F2（种内变异性）	**10**
F3（PoD 研究持续时间：4 个月）	**急性可接受暴露水平为 1**
	慢性 PDE 为 5
F4（无严重毒性）	**1**
F5 (NOEL)	**1**
F6（PoD 途径外推）	**不适用**
急性可接受暴露水平 = 5 mg/kg/天 x 50 kg / (12 x 10 x 1 x 1 x 1) = 2.1 mg x 1000 µg/mg = 2100 µg/天	
慢性 PDE = 5 mg/kg/天 x 50 kg / (12 x 10 x 5 x 1 x 1) = 0.42 mg x 1000 µg/mg = 420 µg/天	

注射可接受暴露水平和 PDE

在缺乏注射重复给药毒性研究数据的情况下，采用相同 PoD 研究的数据推导包含生物利用度校正因子（F6）的注射给药 PDE。报告显示，未结合的 BPA 在大鼠中的口服全身生物利用度为 2.8%，在小鼠、猴和犬中则小于 1%（ANSES，2013 年）。

注射给药计算	
POD	**5 mg/kg/天**
BW	**50 kg**
F1（小鼠）	**12**
F2（种内变异性）	**10**

F3（PoD 研究持续时间：4 个月）	**急性可接受暴露水平为 1**
	慢性 PDE 为 5
F4（无严重影响）	**1**
F5 (NOEL)	**1**
F6（小鼠口服生物利用度<1%）	**100**
急性可接受暴露水平 = 5 mg/kg/天 x 50 kg / (12 x 10 x 1 x 1 x 1 x 100) = 0.021 mg x 1000 µg/mg = 21 µg/天	
慢性 PDE = 5 mg/kg/天 x 50 kg / (12 x 10 x 5 x 1 x 1 x 100) = 0.0042 mg x 1000 µg/mg = 4.2 µg/天	

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国际人用药品注册技术协调会

ICH 协调指导原则

ICH Q3E：可提取物与浸出物指导原则

支持性文件：3 类浸出物专论

草案

2025 年 8 月 1 日签署

目前为公开征求意见阶段

在 ICH 进程的第 2 阶段，ICH 大会按照国家或地区程序，将相应 ICH 专家工作组商定的共识草案文本或指导原则转交给 ICH 地区的监管机构，供内部和外部征求意见。

ICH Q3E：可提取物与浸出物指导原则

支持性文件：3 类浸出物专论

文件历史

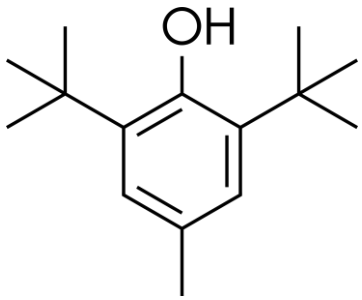
编码	历史	日期
Q3E	在第 2a/b 阶段中获得 ICH 大会监管成员批准，发布以公开征求意见。	2025 年 8 月 1 日
Q3E 支持性文件	在第 2 阶段中获得 ICH 大会监管成员批准，与 ICH Q3E：可提取物与浸出物指导原则一并发布以公开征求意见。	2025 年 8 月 1 日

ICH Q3E：可提取物与浸出物指导原则

支持性文件：3类浸出物专论

目录

2,6-二叔丁基-4-甲基苯酚（BHT）



BHT（CAS 号 128-37-0）的急性可接受暴露水平和慢性 PDE 汇总

BHT		
给药途径	**口服给药（µg/天）**	**注射给药（µg/天）**
急性*	**25,000**	**12,500**
慢性	**25,000**	**12,500**

*急性可接受暴露水平适用于≤1 个月的每日给药

前言

2,6-二叔丁基-4-甲基苯酚，通常称为二丁基羟基甲苯（BHT），是一种合成的抗氧化剂和/或稳定剂，广泛用于食品、化妆品、制药和石油工业使用的聚合物中（经合组织，2002 年；世卫组织，1986 年）。据观察，BHT 是一种与药品生产和包装组件/系统相关的浸出物或可提取物（Parris 等人，2020 年）。

安全性总结

毒性	是	否
致突变性		X
极强效或强效皮肤致敏物		X
皮肤和眼刺激性	X（轻微）	
全身毒性	X（肝脏和肾上腺）	

粮农组织/世卫组织食品添加剂联合专家委员会（JECFA，1996 年）确定了每日允许摄入量（ADI）为 0-0.3 mg/kg/天；与欧洲食品安全局（EFSA）0.25 mg/kg/天的每日允许摄入量一致（EFSA，2012 年）。

限制性毒性

可接受暴露水平和 PDE 的依据	
PoD 研究:	符合 GLP 标准的掺食给药两代和致癌性研究（EFSA 也选用该研究推导 ADI 值）
种属:	大鼠
剂量:	25 mg/kg/天、100 mg/kg/天和 500 mg/kg/天（F0 代）直至哺乳期结束。除高剂量组为 250 mg/kg/天外，F1 代各组给予相同剂量，直至 141-144 周
观察结果和限制性毒性:	在≥100 mg/kg/天的剂量下观察到的肝脏（相对重量增加，肝酶和总细胞色素 P450 含量出现具有统计学意义的增加，组织病理学相关性）和肾上腺组织病理学结果
PoD:	NOAEL = 25 mg/kg/天
参考文献:	McFarlane 等人，1997 年

口服可接受暴露水平和 PDE:

口服计算	
PoD	25 mg/kg/天
BW	50 kg
F1（大鼠）	5
F2（种内变异性）	10
F3（PoD 研究持续时间：22 个月）	急性可接受暴露水平为 1
	慢性 PDE 为 1
F4（肝脏检查结果）	1
F5（NOAEL）	1
F6（PoD 途径外推）	不适用
F7（交叉参照）	不适用
急性可接受暴露水平 = 25 mg/kg/天 x 50 kg / (5 x 10 x 1 x 1 x 1) = 25 mg x 1,000 µg/mg = **25,000 µg/天**	
慢性 PDE = 25 mg/kg/天 x 50 kg / (5 x 10 x 1 x 1 x 1) = 25 mg x 1,000 µg/mg = **25,000 µg/天**	

注射可接受暴露水平和 PDE:

在缺乏注射重复给药毒性研究数据的情况下，采用口服 PoD 研究的数据推导包含生物利用度校正因子（F6）的注射给药值。肝脏和肾上腺检查结果证明，重复掺食给药后，BHT 具有系统性生物利用度。此外，计算机模拟预测的吸收率和经口生物利用度分别为:

- 人类：98.4%和 51.8%
- 大鼠：95.3%和 49.1%

根据证据权重，F6 设为 2。

非胃肠道给药计算	
PoD	25 mg/kg/天
BW	50 kg
F1（大鼠）	5
F2（种内变异性）	10
F3（PoD 研究持续时间：22 个月）	急性可接受暴露水平为 1
	慢性 PDE 为 1
F4（肝脏检查结果）	1
F5（NOAEL）	1
F6（全身毒性和生物利用度：预测值）	2
F7（交叉参照）	不适用
急性可接受暴露水平 = 25 mg/kg/天 x 50 kg / (5 x 10 x 1 x 1 x 1 x 2) = 12.5 mg x 1,000 µg/mg = **12,500 µg/天**	
慢性 PDE = 25 mg/kg/天 x 50 kg / (5 x 10 x 1 x 1 x 1 x 2) = 12.5 mg x 1,000 µg/mg = **12,500 µg/天**	

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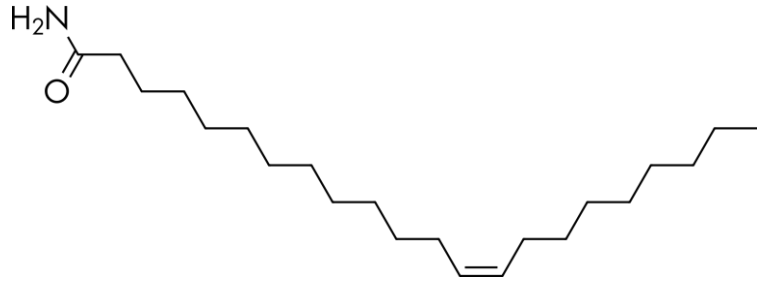
芥酸酰胺



芥酸酰胺（CAS 号 112-84-5）的急性可接受暴露水平和慢性 PDE 汇总

芥酸酰胺		
给药途径	**口服给药（μg/天）**	**注射给药（μg/天）**
急性*	**1,000,000**	**100,000**
慢性	**200,000**	**20,000**

*急性可接受暴露水平适用于≤1 个月的每日给药

前言

芥酸酰胺是一种初级脂肪酰胺，由芥酸羧基与氨缩合而成，通常作为滑爽剂用于塑料制造业（加拿大卫生部，2019 年）。据观察，芥酸酰胺是一种与药品生产和包装组件/系统相关的潜在浸出物。

安全性总结

毒性	是	否
致突变性		X
极强效或强效皮肤致敏物		X
皮肤和眼刺激性		X
全身毒性	X	

限制性毒性

可接受暴露水平和 PDE 的依据	
PoD 研究:	符合 OECD 408 和 GLP 标准的 90 天经口灌胃毒性研究
种属:	大鼠
剂量:	100 mg/kg/天、300 mg/kg/天和 1,000 mg/kg/天（标示剂量）
观察结果和限制性毒性:	在任何剂量下均未观察到给药相关不良反应。
PoD:	NOAEL = 1,000 mg/kg/天
参考文献:	ECHA, 2023

口服可接受暴露水平和 PDE:

口服计算	
PoD	1,000 mg/kg/天
BW	50 kg
F1（大鼠）	5
F2（种内变异性）	10
F3（PoD 研究持续时间：90 天）	急性可接受暴露水平为 1
	慢性 PDE 为 5
F4（无严重毒性）	1
F5（NOAEL）	1
F6（PoD 途径外推）	不适用
F7（交叉参照）	不适用
急性可接受暴露水平 = 1,000 mg/kg/天 x 50 kg / (5 x 10 x 1 x 1 x 1) = 1,000 mg x 1000 µg/mg = **1,000,000（µg/天）**	
慢性 PDE = 1,000 mg/kg/天 x 50 kg / (5 x 10 x 5 x 1 x 1) = 200 mg x 1,000 µg/mg = **200,000（µg/天）**	

注射可接受暴露水平和 PDE:

在缺乏注射重复给药毒性研究数据的情况下，基于芥酸酰胺的理化特性（MW = 337.6 g/mol，预测 LogP 8.8），采用口服 PoD 研究的数据推导包含生物利用度校正因子（F6）的注射给药 PDE。因此，F6 设为 10。

非胃肠道给药计算	
PoD	1,000 mg/kg/天
BW	50 kg
F1（大鼠）	5
F2（种内变异性）	10

F3（PoD 研究持续时间：90 天）	急性可接受暴露水平为 1
	慢性 PDE 为 5
F4（无严重毒性）	1
F5（NOAEL）	1
F6（理化特性）	10
F7（交叉参照）	不适用
急性可接受暴露水平 = 1,000 mg/kg/天 x 50 kg / (5 x 10 x 1 x 1 x 1 x 10) = 100 mg x 1000 µg/mg = **100,000（µg/天）**	
慢性 PDE = 1,000 mg/kg/天 x 50 kg / (5 x 10 x 5 x 1 x 1 x 10) = 20 mg x 1,000 µg/mg = **20,000（µg/天）**	

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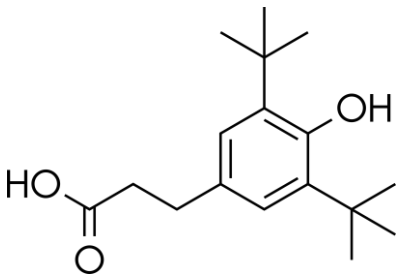
3-(3,5-二叔丁基-4-羟基苯基)丙酸（Irganox 1310）



Irganox 1310（CAS 号 20170-32-5）的急性可接受暴露水平和慢性 PDE 汇总

Irganox 1310		
给药途径	**口服给药（μg/天）**	**注射给药（μg/天）**
急性*	**300,000**	**300,000**
慢性	**30,000**	**30,000**

*急性可接受暴露水平适用于≤1 个月的每日给药

前言

3,5-二叔丁基-4-羟基苯基丙酸（商品名：Irganox 1310）是一种苯基丙酸，是抗氧化剂季戊四醇四（3-（3,5-二叔丁基-4-羟基苯基）丙酸酯（商品名：Irganox 1010）的水解降解产物。Irganox 1010 常被添加于药品包装组件/系统使用的聚合材料中，如医用输液袋，以增强稳定性并防止老化。据观察，Irganox 1310 是一种与药品生产和包装组件/系统相关的浸出物（Zhang F 等人，2016 年；Tao B 等人，2020 年）。

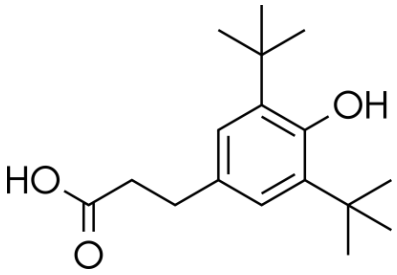
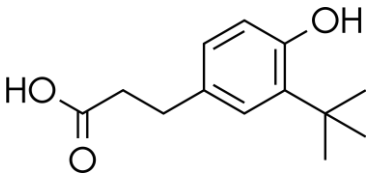
安全性总结

毒性	**是**	**否**
致突变性*		X
极强效或强效皮肤致敏物*		X
皮肤和眼刺激性*	X （苯酚结构基团）	
全身毒性**		X

*基于计算机模拟预测

**基于替代结构重复给药毒性数据

尚无有关 Irganox 1310 的毒性研究数据；但是，有结构相近类似物 3-(3-叔丁基-4-羟基苯基)丙酸的研究数据，Tanimoto 相似性评分为 98.5%（PubChem，2024 年；REACH，2014 年）。3-(3-叔丁基-4-羟基苯基)丙酸比 Irganox 1310 少一个叔丁基，这预计会降低空间位阻，从而产生更具反应性的苯酚。不需要额外的校正因子。

	浸出物	替代物
名称	**3,5-二叔丁基-4-羟基苯丙酸（Irganox 1310）**	**3-(3-叔丁基-4-羟基苯基)丙酸**
结构		
CAS#	20170-32-5	107551-67-7
分子量（g/mol）	278.4	222.28
Log P	4.7	3

替代物限制性毒性

可接受暴露水平和 PDE 的依据	
PoD 研究:	符合 OECD 407 标准的 28 天经口灌胃毒性研究
种属:	大鼠
剂量:	10 mg/kg/天、50 mg/kg/天和 300 mg/kg/天
观察结果和限制性毒性:	在任何剂量下均未观察到给药相关不良反应。
PoD:	NOAEL = 300 mg/kg/天
参考文献:	REACH，2014 年

口服可接受暴露水平和 PDE:

口服计算	
PoD	300 mg/kg/天
BW	50 kg
F1（大鼠）	5
F2（种内变异性）	10
F3（PoD 研究持续时间：28 天）	急性可接受暴露水平为 1
	慢性 PDE 为 10
F4（无严重毒性）	1
F5（NOAEL）	1
F6（PoD 途径外推）	不适用
F7（替代物选择）	1
急性可接受暴露水平 = 300 mg/kg/天 x 50 kg / (5 x 10 x 1 x 1 x 1 x 1) = 300 mg x 1,000 µg/mg = **300,000（µg/天）**	

慢性 PDE = 300 mg/kg/天 x 50 kg / (5 x 10 x 10 x 1 x 1 x 1) = 30 mg x 1000 µg/mg = **30,000（µg/天）**

注射可接受暴露水平和 PDE:

在缺乏注射重复给药毒性研究数据的情况下，采用口服 PoD 研究的数据推导包含生物利用度校正因子（F6）的注射给药 PDE。计算机模拟预测的吸收率和经口生物利用度分别为 100%和 95.6%。

非胃肠道给药计算	
PoD	300 mg/kg/天
BW	50 kg
F1（大鼠）	5
F2（种内变异性）	10
F3（PoD 研究持续时间：28 天）	急性可接受暴露水平为 1
	慢性 PDE 为 10
F4（无严重毒性）	1
F5（NOAEL）	1
F6（理化特性）	1
F7（替代物选择）	1
急性可接受暴露水平 = 300 mg/kg/天 x 50 kg / (5 x 10 x 1 x 1 x 1 x 1 x 1) = 300 mg x 1000 µg/mg = **300,000（µg/天）**	
慢性 PDE = 300 mg/kg/天 x 50 kg / (5 x 10 x 10 x 1 x 1 x 1 x 1) = 30 mg x 1000 µg/mg = **30,000（µg/天）**	

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Binding Potency h-CLAT" and "Respiratory sensitization". Predictions performed: 1-25-25.

OECD QSAR Toolbox. Version 4.5 SP1. Prediction results of 3-(3,5-Di-tert-butyl-4-hydroxyphenyl) propanoic acid (CAS 20170-32-5) for profilers: "Eye irritation/corrosion Inclusion rules by BfR" and "Skin irritation/ corrosion Inclusion rules by BfR". Predictions performed: 1-25-25.

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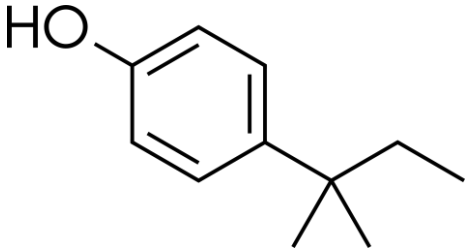
4-叔戊基苯酚



4-叔戊基苯酚（CAS 号 80-46-6）的急性可接受暴露水平和慢性 PDE 汇总

4-叔戊基苯酚		
给药途径	口服给药（µg/天）	注射给药（µg/天）
急性*	**50,000**	**25,000**
慢性	**5,000**	**2,500**

*急性可接受暴露水平适用于≤1 个月的每日给药

前言

4-叔戊基苯酚是一种烷基化苯酚，用作清洁剂中的抑菌剂，以及合成橡胶、塑料材料和树脂制造中的抗氧化剂和紫外线稳定剂（PubChem，2024 年；AICIS 报告，2021 年）。据观察和报告，它是包装组件/系统的浸出物。

安全性总结

毒性	是	否
致突变性		X
极强效或强效皮肤致敏物		X
皮肤和眼刺激性	X	
全身毒性	X 体重增长下降 10% - 50%	

4-叔戊基苯酚是一种已知的环境内分泌干扰物，对人类健康无内分泌干扰作用，因此该终点不被视为限制性毒性（ECHA，2021 年）。

限制性毒性

可接受暴露水平和 PDE 的依据	
PoD 研究:	经口给药产前发育毒性研究
种属:	大鼠
剂量:	0 mg/kg/天、50 mg/kg/天、200 mg/kg/天和 500 mg/kg/天，妊娠第 6-15 天给药
观察结果和限制性毒性:	母体毒性 ≥ 200 mg/kg/天（脱毛、尿液染色、呼吸音异常、软便发生率增加，体重增长和摄食量下降 10% - 50%）。在 500 mg/kg/天剂量下，出现继发于母体毒性的胎仔效应（肋骨弯曲和胎仔体重下降 6%）
PoD:	母体毒性的 NOAEL 为 50 mg/kg/天，发育毒性的 NOAEL 为 200 mg/kg/天。
参考文献:	EA，2008 年；AICIS，2021 年

口服可接受暴露水平和 PDE:

口服计算	
PoD	50 mg/kg/天
BW	50 kg
F1（大鼠）	5
F2（种内变异性）	10
F3（PoD 研究持续时间：妊娠第 6-15 天）	急性可接受暴露水平为 1
	慢性 PDE 为 10
F4（无严重毒性）	1
F5（NOAEL）	1
F6（PoD 途径外推）	不适用
F7（交叉参照）	不适用
急性可接受暴露水平 = 50 mg/kg/天 x 50 kg / (5 x 10 x 1 x 1 x 1) = 50 mg x 1,000 µg/mg = **50,000（µg/天）**	
慢性 PDE = 50 mg/kg/天 x 50 kg / (5 x 10 x 10 x 1 x 1) = 5 mg x 1,000 µg/mg **= 5000（µg/天）**	

注射可接受暴露水平和 PDE:

在缺乏注射重复给药毒性研究数据的情况下，采用口服 PoD 研究的数据推导包含生物利用度校正因子（F6）的注射给药值。计算机模拟预测的吸收率和经口生物利用度分别为 100%和 61.7%。因此，F6 设为 2。

非胃肠道给药计算	
PoD	50 mg/kg/天

BW	50 kg
F1（大鼠）	5
F2（种内变异性）	10
F3（PoD 研究持续时间：妊娠第 6-15 天）	急性可接受暴露水平为 1
	慢性 PDE 为 10
F4（无严重毒性）	1
F5（NOAEL）	1
F6（生物利用度：预测值）	2
F7（交叉参照）	不适用
急性可接受暴露水平 = 50 mg/kg/天 x 50 kg / (5 x 10 x 1 x 1 x 1 x 2) = 25 mg x 1,000 µg/mg = **25,000（µg/天）**	
慢性 PDE = 50 mg/kg/天 x 50 kg / (5 x 10 x 10 x 1 x 1 x 2) = 2.5 mg x 1,000 µg/mg = **2500（µg/天）**	

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Candidate List of substances of very high concern for Authorisation
(published in accordance with Article 59(10) of the REACH Regulation)
https://echa.europa.eu/candidate-list-table/-/dislist/details/0b0236e180e22a96

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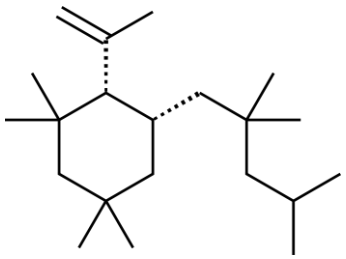
顺式-1,1,5,5-四甲基-2-(1-甲基乙烯基)-3-(2,2,4-三甲基戊基)-环己烷
（橡胶低聚物 $C_{21}H_{40}$）



橡胶低聚物 $C_{21}H_{40}$（CAS 号 114123-73-8）的急性可接受暴露水平和慢性 PDE 汇总

（橡胶低聚物 $C_{21}H_{40}$）		
给药途径	**口服给药（μg/天）**	**注射给药（μg/天）**
急性*	**100,000**	**10,000**
慢性	**10,000**	**1,000**

*急性值适用于≤ 1 个月的每日给药

前言

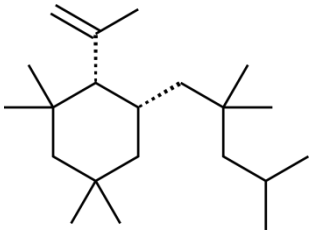
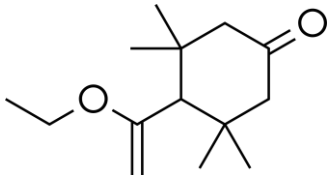
顺式-1,1,5,5-四甲基-2-(1-甲基乙烯基)-3-(2,2,4-三甲基戊基)-环己烷（也称为橡胶低聚物 $C_{21}H_{40}$）属于倍半萜类有机化合物。这些化合物是含有三个连续异戊二烯单元的萜烯（Feunang 等人，2016 年）。橡胶低聚物 $C_{21}H_{40}$ 是一种用于制备丁基橡胶和异戊二烯共聚反应的低聚物（Chemical Book，2023 年）。据观察，橡胶低聚物 $C_{21}H_{40}$ 是一种与药用橡胶生产和包装组件相关的浸出物或可提取物。

安全性总结

毒性	是	否
致突变性*		X
极强效或强效皮肤致敏物*		X
皮肤和眼刺激性*		X
全身毒性**		X

*基于计算机模拟预测
**基于替代结构重复给药毒性数据

目前尚无有关橡胶低聚物 $C_{21}H_{40}$ 的全身毒性研究数据；但是，利用美国 EPA 相似物识别法（AIM，2025 年）测定了结构相近类似物 3,3,5,5-四甲基-4-乙氧基乙烯基环己酮，并将其选为 PDE 推导的替代品。基于下文所示 MW 和 Log P 理化特性，采用了从经口给药外推到非胃肠道给药的暴露校正因子 F6=10。对于交叉参照的替代结构选择，无需额外的校正因子。

	浸出物	替代物
名称	橡胶低聚物 $C_{21}H_{40}$	**3,3,5,5-四甲基-4-乙氧基乙烯基环已酮**
结构		
CAS#	**114123-73-8**	**36306-87-3**
分子量（g/mol）	**292.5**	**224.34**
Log P	**8.8**	**3.1**

替代物限制性毒性

可接受暴露水平和 PDE 的依据	
PoD 研究:	符合 OECD 422 标准的膳食联合重复给药毒性研究与生殖/发育毒性筛选试验
种属:	大鼠
剂量:	1,500、5,000 和 15,000 ppm 或 97,323,970 mg/kg/天。雄性在交配前、交配期间各暴露 2 周，直至处死（共 29 天）。雌性在交配前、交配期间、交配后各暴露 2 周和哺乳期至少暴露 4 天（共 41-47 天）
观察结果和限制性毒性:	肾脏（肉眼可见和组织学相关的透明小滴蓄积和颗粒管型）、肝脏（肉眼可见的结果和肝细胞肥大）、脾脏（绝对重量和相对重量）以及摄食量和体重减少
PoD:	NOAEL = 97-103 mg/kg/天
参考文献:	Api 等人，2021 年

口服可接受暴露水平和 PDE:

口服计算	
PoD	100 mg/kg/天
BW	50 kg
F1（大鼠）	5
F2（种内变异性）	10
F3（PoD 研究持续时间：29 天）	急性可接受暴露水平为 1
	慢性 PDE 为 10
F4（无严重毒性）	1

F5（NOAEL）	1
F6（PoD 途径外推）	不适用
F7（替代物选择）	1
急性可接受暴露水平 = 100 mg/kg/天 x 50 kg / (5 x 10 x 1 x 1 x 1 x 1) = 100 mg x 1,000 µg/mg = **100,000（µg/天）**	
慢性 PDE = 100 mg/kg/天 x 50 kg / (5 x 10 x 10 x 1 x 1 x 1) = 10 mg x 1,000 µg/mg = **10,000（µg/天）**	

注射可接受暴露水平和 PDE:

在缺乏注射重复给药毒性研究数据的情况下，采用口服 PoD 研究的数据推导包含生物利用度校正因子（F6）的注射给药 PDE。计算机模拟预测的吸收率和经口生物利用度分别为 100%和 95.6%。

非胃肠道给药计算	
PoD	100 mg/kg/天
BW	50 kg
F1（大鼠）	5
F2（种内变异性）	10
F3（PoD 研究持续时间：29 天）	急性可接受暴露水平为 1
	慢性 PDE 为 10
F4（无严重毒性）	1
F5（NOAEL）	1
F6（理化特性）	10
F7（替代物选择）	1
急性可接受暴露水平 = 100 mg/kg/天 x 50 kg / (5 x 10 x 1 x 1 x 1 x 10 x 1) = 100 mg x 1,000 µg/mg = **10,000（µg/天）**	
慢性 PDE = 100 mg/kg/天 x 50 kg / (5 x 10 x 10 x 1 x 1 x 1 x 10 x 1) = 100 mg x 1,000 µg/mg = **1,000（µg/天）**	

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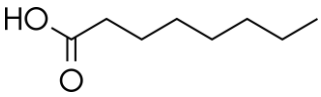
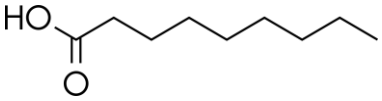
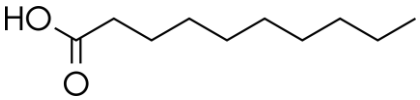
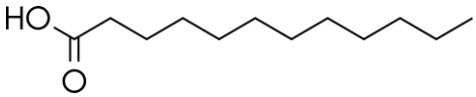
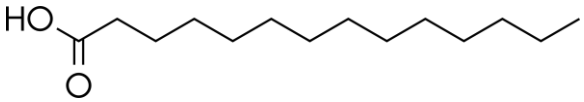
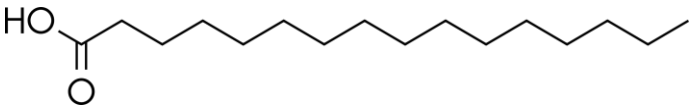
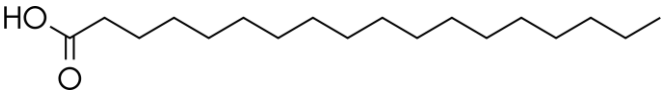
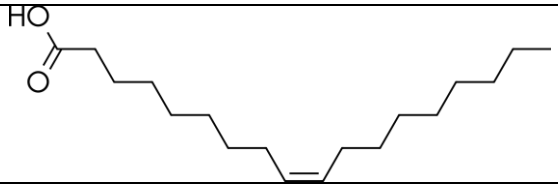
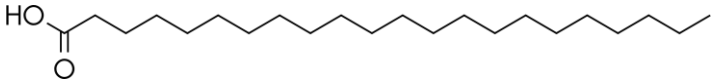
常见脂肪酸浸出物（C12-C22）

化学名称（CAS 号）	结构
辛酸（C8） 124-07-5	
壬酸（C9） 112-05-0	
癸酸（C10） 334-48-5	
月桂酸（C12） 57-10-3	
肉豆蔻酸（C14） 544-63-8	
棕榈酸（C16） 57-10-3	
硬脂酸（C18） 57-11-4	
油酸（C18） 112-80-1	
山嵛酸（C22） 112-85-6	

前言

脂肪酸通常定义为无支链的脂肪族长链羧酸，该脂肪族链的碳原子数通常为偶数。脂肪族链可以是饱和的（即碳原子仅以单键连接）、单不饱和的（即含有一个双键）或多不饱和的（即含有两个或多个双键）。本专论涵盖链长为 C8 至 C22 的不饱和以及单不饱和脂肪酸。脂肪酸是内源性物质，在饮食中普遍存在。脂肪酸也常被用作药品生产的原料，并且据观察是包装组件/系统的浸出物和可提取物（Jolly 等人，2022 年）。

游离脂肪酸可能存在于全肠外营养液和静脉注射脂质乳剂中。此外，月桂酸、肉豆蔻酸、棕榈酸、硬脂酸和油酸在口服暴露下被认定为“公认安全”（GRAS）或 GRAS 物质的成分（美国食品药品监督管理局（FDA），2018 年），除月桂酸外，其余均已被列

入 FDA 非活性成分数据库，在已获批制剂（各种给药途径和剂型）中使用。硬脂酸（添加量 4000 ppm）也被欧洲委员会（1974 年）列入了人工调味物质清单，可添加到食品中而不会危害公众健康。

安全性总结

现有数据表明，脂肪酸 C8-C22 具有低度至中度急性毒性；无致突变性；非皮肤致敏物，对家兔的皮肤和眼睛无刺激性。关键的重复给药毒性研究汇总如下。

壬酸（C9）毒性研究汇总	
研究:	符合 OECD 407 和 GLP 标准的 28 天经口毒性研究
种属:	大鼠
剂量:	50 mg/kg/天、100 mg/kg/天和 1,000 mg/kg/天
观察结果和限制性毒性:	未观察到不良全身毒性作用。
NOAEL:	1,000 mg/kg/天
参考文献:	Api 等人，2020 年

山嵛酸（C22）毒性研究汇总	
研究:	符合 OECD 422 标准的经口联合重复给药毒性研究与生殖/发育毒性筛选试验
种属:	大鼠
剂量:	100 mg/kg/天、300 mg/kg/天和 1,000 mg/kg/天
观察结果和限制性毒性:	未观察到不良毒性作用。
NOAEL:	1,000 mg/kg/天（全身和生殖/发育毒性）
参考文献:	Nagao 等人，2002 年

脂肪酸具有共同的降解途径，代谢为乙酰辅酶 A（acetyl-CoA）或其他关键代谢物（结构相似的分解产物）。尽管不同的结构会有不同的反应序列，但不同碳链长度、饱和以及不饱和化合物或支链化合物之间的代谢清除率预计不会有显著差异（CIR，2019 年）。

Jolly 等人（2022 年）综述了八种脂肪酸（包括棕榈酸、硬脂酸、月桂酸和油酸）的现有毒性数据，并提出了非胃肠道给药基于健康的暴露限值（Jolly 等人，2022 年）。关键考虑因素是基于临床非胃肠道给药暴露情况、胶束形成能力以及低密度脂蛋白水平伴随心血管疾病风险增加。此外，还提出了 50 mg/天的非胃肠道给药慢性类特异性值，并认为其适用于多种脂肪酸暴露，包括缺乏毒性数据的脂肪酸。

不饱和或单饱和脂肪酸 C8 至 C22 的可接受暴露量

根据内源性和外源性人体暴露以及非临床暴露数据，脂肪酸被认为急性和慢性毒性较低。结合产品质量考量因素，无论给药途径或暴露持续时间如何，均确定一种或多种 C8 至 C22 脂肪酸的可接受暴露量为≥10 mg/天。

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