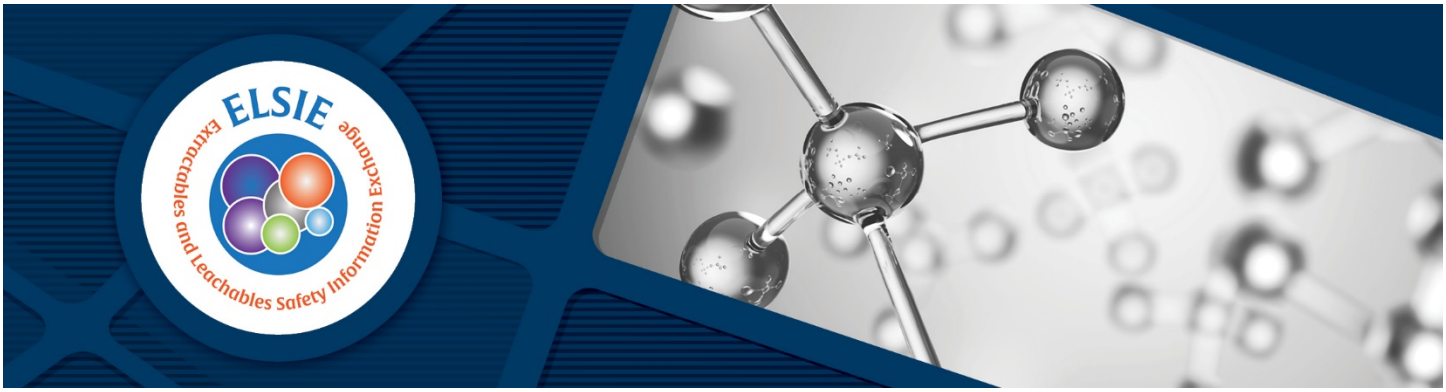

Risk Control

SAFETY ASSESSMENT

OVERVIEW

Safety evaluation of extractables and leachables (E&Ls) is important for the protection of patients inadvertently exposed to compounds from polymeric materials that interact with the drug substance and drug product. The focus of this white paper is to summarize the current regulatory landscape and other publications regarding the safety evaluation of drug substance and drug product impurities and highlight the opportunities that could be addressed with E&L specific guidance documents. Leachables are regarded as a subset of drug impurities and there are existing documents that can be leveraged for risk assessment purposes, summarized in Table 1.

Table 1. Existing guidance documents relevant to impurity or leachables risk assessment.

Guidance, publication, or public communication	Description	Gaps and Limitations
ICHQ3A and Q3B	Qualification framework and limits for non-mutagenic impurities in drug substance (DS; Q3A) and drug product (DP; Q3B).	DS and DP product impurities are related to the active pharmaceutical ingredient (API) as they are part of the manufacturing process or degraded products. E&Ls cannot be qualified by testing in a toxicology study as a percentage of API in the DP. No specific guidance on substances that are known to be toxic e.g., potential sensitizers.
ICHQ3C	Outlines methodology and modifying factors for calculating Permitted Daily Exposure (PDE) for solvents. Derives PDE values for common solvents used in pharmaceutical synthesis. Solvents can also be E&Ls.	Unlike some E&L substances, solvents are widely bioavailable following oral administration, therefore no bioavailability or route of administration considerations are included in PDE derivation.

Guidance, publication, or public communication	Description	Gaps and Limitations
ICHQ3D	Provides framework for deriving PDE values for elemental impurities. Derives oral, parenteral, and inhalation PDE values for elements commonly used in pharmaceutical synthesis. Elemental impurities can also be E&Ls.	Focus is only on elemental impurities. The principles of safety assessment may apply to E&Ls.
ICHM7	Outlines classification framework, limits and details for calculating compound-specific exposure limits for linear and non-linear mutagenic carcinogens. The Addendum provides acceptable intake (AI)/PDE limits for common substances used in pharmaceutical synthesis.	Focus is only on mutagenic and carcinogenic impurities. The principles of safety assessment may apply to E&Ls.
EMA Setting health-based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities	Considers the potential for cross-contamination of medicinal products produced in shared facilities. Recommends an approach for deriving a scientifically based safe threshold value for individual active substances.	Focus is active pharmaceutical ingredients as potential impurities. The principles of deriving safe threshold values may apply to E&Ls.
FDA Control of Nitrosamine Impurities in Human Drugs	Guidance for detection and control of nitrosamine impurities in drug substance/product	Focus is only on nitrosamines. The principles of safety assessment may apply to E&Ls.
EMA Nitrosamine impurities in human medicinal products	Guidance for detection and control of nitrosamine impurities in drug substance/product	Focus is only on nitrosamines. The principles of safety assessment may apply to E&Ls.
Health Canada Request to evaluate the risk of the presence N-nitrosamine impurities in human pharmaceutical products	Guidance for detection and control of nitrosamine impurities in drug substance/product	Focus is only on nitrosamines. The principles of safety assessment may apply to E&Ls.
Swiss Medic Potential nitrosamine contamination: request to perform a risk evaluation	Guidance for detection and control of nitrosamine impurities in drug substance/product	Focus is only on nitrosamines. The principles of safety assessment may apply to E&Ls.

Guidance, publication, or public communication	Description	Gaps and Limitations
ISO 10993-17	Provides methodology for establishing allowable limits for leachable substances for medical devices.	For medical device only, and relevance for drug/device combination products is uncertain. Safety approach applies different assumptions and safety factors than pharmaceutical-related guidelines ICH Q3C, Q3D, and M7.
USP <1664> (2014)	Provides framework for assessment of drug product leachables that are associated with pharmaceutical packaging/delivery systems.	No specific guidance provided for individual compound safety assessment.
Ball et al. (2007)	Product Quality Research Institute (PQRI) safety qualification thresholds and their use in orally inhaled and nasal drug product evaluation.	Specific E&Ls for inhaled products. Safety Concern Threshold based on carcinogenicity is 10-fold lower than recommended by ICH M7.
Paskiet (2018)(PQRI workshop); Ball (2018)(PQRI workshop)	PQRI proposed safety thresholds for parenteral drug products.	Results of the analysis are only in slide format. The database behind proposed limits are not publicly available for validation.
Li et al. (2015)	E&L framework for biotechnology products.	For biotechnology products only. Safety principles for E&Ls may be applicable to other drug-device combinations.
Broschard et al. (2016)	Safety assessment framework and two PDEs derived for common E&L substances.	No specific guidance on substances that are potential sensitizers.
Bercu et al. (2018)	Compound-specific limits for 20 synthetic reagents and by-products, and a class-specific toxicology limit for alkyl bromides.	Intended for process-related impurities, but safety principles could be applied to E&Ls.
Ball and Beierschmitt (2020)	Development and use of PDE values in the risk assessment process	No guidance for data poor substances
Kroes et al. (2004)	Provides structure based threshold of toxicological concern (TTC) process for application of substances present at low levels in the diet.	Intended for food-based chemicals; chemical space for E&Ls is unknown.

Guidance, publication, or public communication	Description	Gaps and Limitations
Munro et al. (1996)	Cramer classification and limits for non-mutagenic substances when toxicity data is unavailable.	Unknown applicability to the chemical space for E&Ls. Intended for oral compounds.
Patlewicz et al. (2008)	In silico application of Cramer classification using Toxtree to derive non-mutagenic limits for compounds when toxicity data is unavailable.	Unknown applicability to the chemical space for E&Ls. Intended for oral compounds.
U.S. Food and Drug Administration Center for Drug Evaluation and Research Robison (2018) (PQRI Workshop)	Recommendations for identification and qualification of leachables in inhalation and parenteral drug products for marketing application purposes.	Conveyed in meeting presentations; uncertainty with regard to enforceability and consensus across reviewers/divisions; no specific recommendations regarding expectations/methods to evaluate sensitization and irritation endpoints in decision tree.
Ophthalmic products McGovern (2018); Mellon (2019) Lewis, 2011 (AAPS Workshop)	Current FDA Perspective on leachable impurities in parenteral and ophthalmic drug products.	Thresholds are in relative concentration units rather than dose per day. Based on an oral presentation, and no guidelines developed.
TR 133-1 – The ECETOC Conceptual Framework for Polymer Risk Assessment (CF4Polymers) European Centre for Ecotoxicology and Toxicology of Chemicals (2019)	Guiding principles and considerations for risk assessment of polymer products.	Unknown applicability to E&Ls relevant to clinical space.

The key aspects of existing impurity safety assessment guidance and specific considerations for leachables will be highlighted below.

WHAT IS NEEDED?

Framework for safety assessment of E&Ls

In general, the safety assessment approaches for E&Ls are consistent with that described for drug product and substance manufacturing process-related impurities. Therefore, building on existing guidelines, publications by Broschard et al. (2016) and Parris et al. 2020 (under revision) propose a safety evaluation process flow which relies on understanding the overall toxicological profile, including mutagenic potential to inform an appropriate control strategy. Leachables identified above an appropriate analytical threshold can be assessed for mutagenicity and other toxicity endpoints as shown in Figure 1.

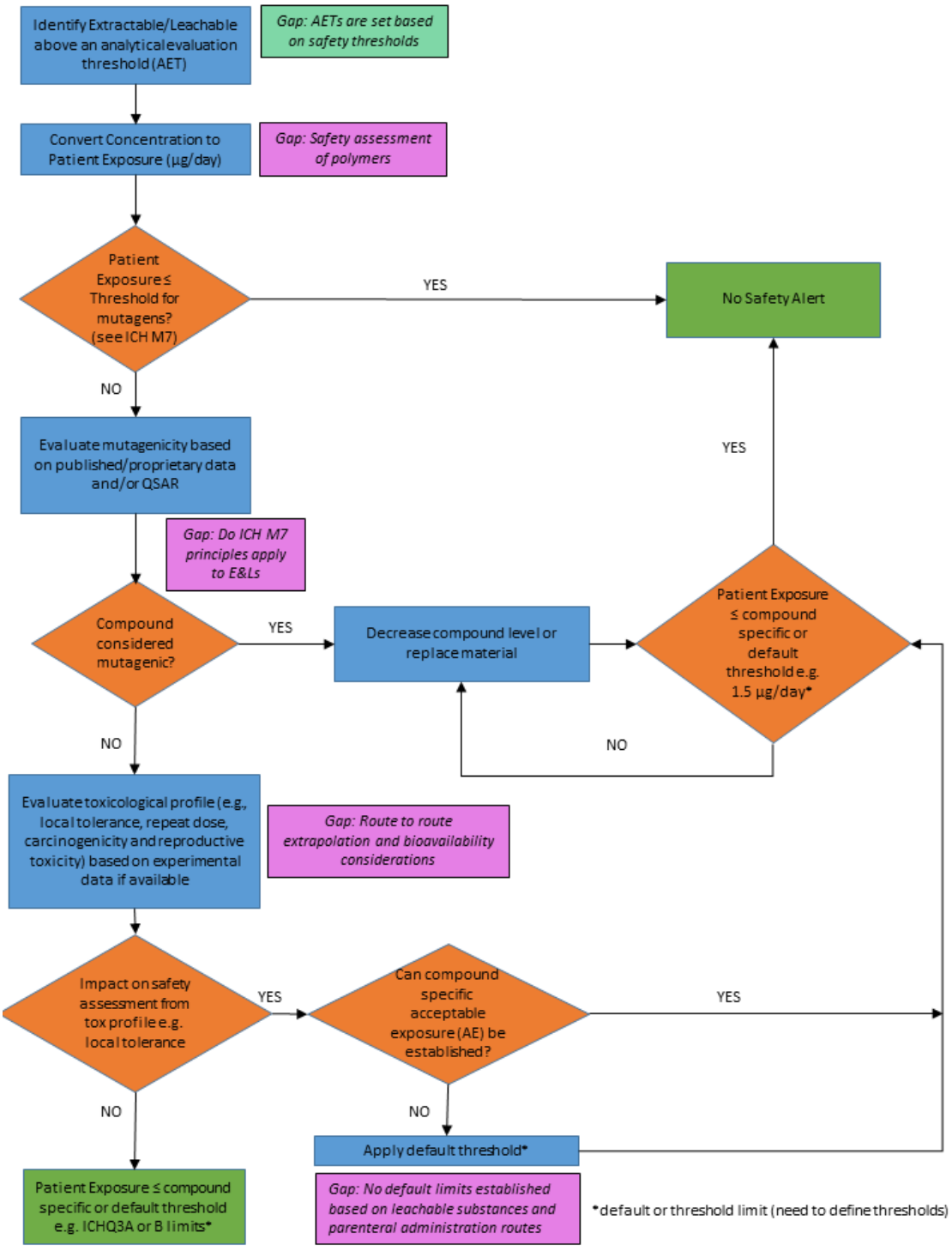

Figure 1. Example extractable/leachable safety evaluation process for a non-biologic parenteral, oral, or topical drug product. The flowchart addresses organic extractables/leachables. Note that this flowchart is an example of a suggested approach and highlights some of the specific considerations for E&Ls. It is illustrative of typical approaches, and it is recognized that other approaches can be used. Adapted from Broschard et al. 2016.

SPECIAL CONSIDERATIONS FOR E&LS

Aspects where additional guidance would be helpful in the safety assessment of E&Ls include but are not limited to:

- Use of default thresholds for substances with limited toxicological data (further discussed in Section 4)
- Application of M7 principles to extractables and leachables
- Route of administration and bioavailability considerations
- Evaluating endpoint-specific effects (e.g., irritation, sensitization)
- Intermittent (non-daily) dosing and less than lifetime (LTL) limits for non-mutagenic substances
- Risk assessment of polymers (e.g., monomers and other components)

A general framework for safety assessment of E&Ls includes a review of the available literature, and/or computational toxicology assessment to derive a substance-specific acceptable exposures (AEs). This is well described in Broschard et al. (2016) and Parris et al., 2020 (under review) and worked examples of acceptable exposures for common E&L substances are presented. In the absence of sufficient data, TTC concepts can been used to define acceptable exposures posing negligible risk to patients. Aspects of the framework warrant further consideration and guidance, for example extractable studies are performed based on screening of compounds whereas leachable studies are performed based on targets compounds. The extractable profile is likely to contain peaks that cannot be identified and/or quantified which is challenging for the toxicologist to perform the same level of safety assessment with extractable versus leachable profiles. In addition, computational structure activity relationship (SAR) evaluation of E&Ls may have limited value they can be out of domain of current knowledge, particularly for statistical systems.

EXISTING DEFAULT THRESHOLDS

Default thresholds (i.e., doses where toxicity is not concerning for an untested chemical), are critical to E&Ls which oftentimes are not tested in a toxicity study. Toxicity testing of low-level E&Ls would result in significant animal usage with little value to patient safety. The TTC concept was originally developed for food safety as a pragmatic way to address potentially carcinogenic impurities in food contact materials as the Threshold of Regulation (TOR) by the U.S. Food and Drug Administration (US Food and Drug Administration, 1995). Subsequently, the use of this TTC has been expanded to encompass DNA reactive (mutagenic) impurities in pharmaceuticals and included in ICH M7 (ICH, 2017). TTC and less-than-lifetime (LTL) TTC values for several adverse health endpoints other than mutagenicity have been developed over the years and applied for food safety, pharmaceuticals, and personal healthcare products including those for systemic non-cancer effects (Dolan et al., 2005; Kroes et al., 2004), developmental and reproductive toxicity (Stanard et al., 2015), and dermal and respiratory sensitization (Carthew et al., 2009; Safford et al., 2015; Safford et al., 2011). The TTC can be used to judge whether exposure to a substance is low enough that the probability of adverse health effects is negligible, and no further data collection is necessary. TTCs are not applicable when adequate substance-specific assessment and toxicity data are available or are required under existing regulations (EFSA and WHO, 2016; EFSA Scientific Committee, 2012).

Challenges with the use of TTC and staged TTC approaches for E&L safety assessment include (Olson et al., 2016):

- Whether a chemical being evaluated falls within the applicability domain of the toxicological database used to calculate the particular threshold value
- Route-to-route extrapolation from one route of exposure (e.g., oral toxicity data) being applied to another (e.g., leachable substance in parenteral product)

The selection of a TTC is a crucial step in the safety assessment process and should consider available chemical data, such as structure and chemical class as well the dosing regimen of the drug product in question. For potentially DNA reactive (mutagenic) impurities without carcinogenicity data, ICH M7 establishes an acceptable intake, based on the TTC, of 1.5 µg/day for a lifetime (or LTL AIs for shorter duration exposures). Exposure below this AI is unlikely to exceed a lifetime cancer risk of 1 in 10^5 for a mutagenic substance with unknown carcinogenic potential (ICH, 2017). ICH M7 recognizes a group of high potency mutagenic carcinogens referred to as the "cohort of concern" comprising aflatoxin-like-, N-nitroso-, and alkyl-azoxy compounds, for which acceptable intakes should be justified on a case by case basis.

For non-genotoxic chemicals, a tiered TTC approach may be applied to leachable substances based on potency/toxicity and potential for carcinogenicity. Examples of tiered and non-tiered TTC approaches include Harvey et al. (2017) and Dolan et al. (2005) (pharmaceuticals); Munro et al. (1996) and Kroes et al. (2004) (industrial chemicals and indirect food additives); Ball et al. (2007) and Paskiet et al. (2013) (E&L). The decision for selecting a TTC default value must consider the basis for how the TTC was derived and the relevance to the specific E&L substance being evaluated. For example, the TTC approach described by Dolan et al. (2005) was intended for APIs, but contained API data and also other types of chemicals such as those in the Munro et al. (1996) database or environmental contaminants. Munro et al. (1996) was intended for substances in food, and the relevance to parenteral exposure needs further development. Also, the relationship of these databases to the chemical space of E&Ls need to be further explored.

PQRI and US FDA

The Product Quality Research Institute (PQRI) proposed development of Safety Concern Thresholds (SCTs), and Qualification Thresholds (QT), for extractables and leachables for parenteral drug products (Paskiet et al., 2013). SCTs provide a threshold in which to identify E&Ls. The QT is a safety-based limit of 150 µg/day, where systemic toxicity (i.e., non-cancer) endpoints are not needed for the E&L. It should be acknowledged that substances exceeding the SCT are not necessarily "unsafe." Such situations would need to be dealt with on a case by case basis based on scientific rational, the level of concern and the clinical indication. It should be noted that the SCT is based on mutagenic carcinogenicity, which for ICH M7 the AI is 1.5 µg/day. There are unofficial limits for E&Ls being derived and presented, such as the 50 µg/day limit for systemic toxicity of E&Ls in parenteral products (Paskiet, 2018 workshop presentation). PQRI also propose a threshold value of 5 µg/day for substances with known or suspected sensitization or irritation potential based on *in silico* alerts for dermal or respiratory sensitization. Whilst these limits have been presented orally at a workshop, they have not been formally published and the underlying data behind these limits are unclear. Therefore, the process for selecting the TTC based on route of administration of the pharmaceutical needs more clarity before adoption.

More recently, pharmacology/toxicology representatives from U.S. FDA Centre for Drug Evaluation and Research (CDER) have communicated recommendations or expectations regarding the identification and safety assessment of leachables in marketing applications for parenteral drug products. These recommendations are generally consistent with the PQRI proposal for small-volume parenteral products described above. One important difference is that FDA has not endorsed the 150 or 50 µg/day QT values

for systemic toxicity proposed by PQRI (Paskiet, 2018 workshop presentation; Paskiet et al., 2013) and recommends a 5 µg/day threshold for general toxicity concern instead (McGovern, 2018; Mellon, 2019). This is consistent with the 5 µg/day PQRI concern threshold for sensitization and irritation endpoints, which for implementation purposes results in a single, 5 µg/day QT for all non-cancer concerns. Another notable point made in CDER presentations is that the 1.5 µg/day SCT for parenteral products can, in most cases, also be applied to inhalation products (McGovern, 2018; Robison, 2018). This recommendation is consistent with the principles described in ICH M7 and amends the more conservative 0.15 µg/day SCT described by PQRI for orally inhaled and nasal drug products (OINDPs) in 2007 (Ball et al., 2007).

It should be noted that the CDER recommendations have not been communicated in guidance documents. Therefore, it is unclear if these expectations are enforceable or will be consistently applied among various reviewers and divisions in the FDA. Finally, as shown in Table 2, there have been multiple limits that have been proposed, with different terminology making it difficult to navigate when setting analytical limits or understanding the safety of an untested chemical.

Table 2. Summary of published and orally communicated thresholds proposed for qualification (QT) or to determine the need for safety assessment of leachables (SCT).

Publication or public communication	Default limit
PQRI publication (Ball et al., 2007)	SCT for genotoxicity 0.15 µg/day and QT for sensitization and irritation 5 µg/day for Orally Inhaled and Nasal Drug Product products (OINDP)
PQRI publication (Paskiet et al., 2013)	SCT for genotoxicity 1.5 µg/day, QTs for general toxicity 150 µg/day and for sensitization and irritation 5 µg/day for parenteral and ophthalmic drug products (PODP)
PQRI workshop presentation (Paskiet, 2018)	Proposed QT for general toxicity lowered to 50 µg/day for parenteral products (PDP)
FDA publications (McGovern, 2018; Robison, 2018)	SCT for parenteral and inhalation products 1.5 µg/day
FDA publications (McGovern, 2018; Mellon, 2019)	QT for systemic toxicity, sensitization and irritation 5 µg/day

Establishing Default Limits for Leachables

Default limits (i.e., TTC) have been readily adopted for impurities representing a wide range of chemicals; however, limits specific to leachable substances have not been established. A default or threshold value could be conservatively derived from a database of NOAELs (no-observed-adverse-effect-level) obtained in animal studies conducted for leachable substances representing a wide selection of toxicological endpoints and toxicokinetic effects. This approach would allow the establishment of threshold values based on applicable and relevant data for the assessment of E&L compounds without structural safety concerns and limited or no data, for which well-accepted threshold values already exist. Such limits would avoid overestimation of hazard for E&Ls with moderate to low toxicological concern, as may be anticipated with the conservative threshold recently communicated by the FDA (5 µg/day QT for all non-cancer concerns). Class-specific limits could be developed for common structural classes of E&Ls which are of

lower concern. Sensitization needs to be further explored for its application to the default limit as the current assays were developed for skin sensitization, with limited application to parenteral exposure. Irritation also should be further explored as irritation/corrosion potential is often influenced by the acidic or basic physicochemical properties, which is less relevant for pH-controlled drug products.

The ELSIE consortium database compiles a reference dataset of leachable substances populated with available animal and human toxicity. The database comprises the name, synonyms and CAS number of the leachable substance, study type, species, sex, route of exposure, dose levels, study duration, endpoints reported, NOAEL and/or LOAEL and references. For each leachable substance, the ELSIE database will be reviewed and NOAEL values for relevant toxic effects will be curated and analyzed. The route of administration, species, bioavailability and quality of study will be specifically considered. This project is currently underway within ELSIE with the aim of developing a scientific-based QT approach applicable to non-mutagenic leachable substances.

CONCLUSION

E&Ls are considered a subset of drug impurities and therefore safety assessments should be conducted in accordance with current guidance, where the application of compound-specific or safety-based default threshold values such as TTCs are established (e.g., ICH M7, ICH Q3C and ICH Q3D). There are however specific considerations that apply to E&Ls that would greatly benefit from detailed and harmonized guidance. To support this, ELSIE is leading several scientific efforts to develop best practice in E&L safety risk assessment.

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