Identification and Quantitation Classifications for Extractables and Leachables

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COMMENTARY

Identification and Quantitation Classifications for Extractables and Leachables

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ABSTRACT: Extractables and leachables (E&L) are identified and quantified so that their impact on patient safety can be established and assessed. The uncertainty in the impact assessment is affected by the uncertainty in the substance’s experimentally determined identity and concentration. Thus, these experimentally determined quantities must be reported not only in terms of their absolute result but also in terms of the uncertainty in the result, which is based on the amount and rigor of the information on which the result is based. In this way, the impact assessment can be tempered to account for the uncertainty in its input data. To facilitate the assignment and reporting of uncertainty, classification hierarchies are proposed and discussed for both identification and quantitation. Both hierarchies establish levels or degrees of identification and quantitation based on the uncertainty of the result and contain descriptions of the quality and quantity of information required to achieve a certain level within the hierarchy. The minimal levels that must be achieved to support impact assessment are also established.

KEYWORDS: Extractables, Leachables, Identification, Quantitation, Categorization.

Introduction

During manufacturing, storage and distribution, and use, a packaged pharmaceutical drug product (DP) and its container-closure system (CCS) will chemically interact. Similarly, a medical device will chemically interact with that part of the human body that it contacts, either directly or indirectly, during its clinical use. This interaction will include leaching, wherein substances (called leachables) originally present in the CCS or medical device diffuse into the DP and/or the human body. Corresponding to leachables are extractables, which are substances that are present in the CCS or medical device and which could be leached (that is, are potential leachables).

The purpose of extractables/leachables studies is to either establish those extractables that could leach into the DP or the patient-contacting medium by performing a controlled extraction study on the CCS or establish those leachables that are in the DP or contact medium by performing a migration study. In either case, the extract, the DP, or the contact medium is screened for organic extractables or leachables using chromatographic methods to discover, identify, and quantify these substances. This information is then assessed to establish whether the drug product and its packaging, or the medical device and the patient, are compatible.

The two key characteristics of extractables and leachables that are relevant and necessary in assessing compatibility are:

1. The substance’s identity, as the identity is used to establish the substance’s behavior, characteristics, or properties.

2. The substance’s concentration (in the extract, the DP, or the contact medium), as the magnitude of an extractable’s or a leachable’s effect on an item’s suitability for use is directly related to the amount of the substance that is, or could be, leached.

Although one might think of an extractable’s (or leachable’s) identity and quantity as absolute characteristics (that is, the compound has only one true identity and one accurate quantity), the ways the identities and quantities are experimentally established are prone to certain degrees of uncertainty and correctness. For example, one may have less confidence in a concentration...
estimate obtained via a process based on certain simplifying generalizations and more confidence in a concentration estimate based on rigorous and compound-specific response calibration. Similarly, one may be less confident in an identity based on a single piece of supporting information and more confident if the identity is based on multiple independent and collaborating pieces of information.

When an extractable or leachable is assessed for its potential impact, it is necessary not only to know the outcome of the assessment but also the certainty and confidence one has in the outcome. For example, consider the situation in which the outcome of the assessment is that the packaging system and the DP are marginally compatible. If the assessment is based on input data (identity and concentration) that is highly certain and in which the assessor has high confidence, then the finding of “marginal compatibility” may be adequate and acceptable. On the other hand, if the assessment is based on input data that are uncertain and in which the assessor has low confidence, then the same finding may not be adequate, as there is a wide “margin of error” in the assessment.

For these reasons, identities and concentrations should be reported with information that establishes the certainty and degree of confidence in either the reported identity or concentration. So doing implies that a classification hierarchy has been developed for both identification and quantitation.

The purpose of this Correspondence is to establish and justify such hierarchies and to demonstrate their use in impact assessment.

Identification Classification

The term “identification” is defined as the process of assigning a molecular structure, a chemical name, or other identifying information to an organic compound, or assigning constituent elements or compound structure as appropriate, and a chemical name to an inorganic compound. It is clear that the analytical methods used to secure an identification do not directly provide an identity; rather, a substance’s identity is inferred based on the interpretation of the analytical data that are available for the substance. The amount of detail contained within the identity and the likelihood that the identity is correct increase in direct proportion to the amount of collaborating data and the information content of the data. In the absence of collaborating data or in cases when the identifying information content of the test method is poor (for example, a UV absorption spectrum), an established identity may not be specific (for example, a compound class may be established but the exact member of the class cannot be ascertained) and/or the likelihood that the identity is correct is low. On the other hand, having multiple pieces of collaborating data or when the information content is high (for example, an electron impact ionization mass spectrum illustrating a significant fragmentation pattern) produces an established identity that may be highly specific (specifying an exact compound) and which is likely to be correct.

The proper use of an extractable’s identity requires that an extractable’s or a leachable’s identity be reported in a manner that conveys the status of the identity with respect to its level of detail and accuracy. This is true because the validity of an assessment based on the identity is only as strong as the validity of the identity it is based on. If the identification is tentative, and thus of lower certainty and validity, then assessment based on the identity will be tentative and of lower certainty. However, if one is certain that the identity is correct because the inferred identity has been confirmed, then the assessment based on that identity will most likely be correct.

To this end, identification classes have been proposed and justified. For example, in their Recommendations Document for Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products, the PQRI Leachables and Extractables Working Group proposed three levels of identification—tentative, confident, and confirmed—and provided guidelines for establishing what analytical data were required to achieve and justify each identification level (1). A fourth level, unidentified or unknown, can readily be envisioned (2). Such a classification has been captured in the USP monograph on extractables, <1663> (3).

Though useful, the USP classification can be awkward to use. For example, consistent with its common definitions and data reporting practices, the term tentative implies that a compound has been sufficiently identified that a name and CAS registry number (RN) can be provided, with the caveat that one is just not very confident that this is the right identity (although frankly this caveat is not typically expressed or acknowledged, and tentatively identified compounds are impact assessed as if the provided identity were certain). The way it is
defined by both PQRI and the USP, the term tentative is used to mean identities that are not “firm” enough to establish the exact compound but are sufficient only to establish a compound’s general functionalities. More grammatically correct, such an identity is a partial identification. Moreover, the category that now is referred to as tentative (meaning a name and CAS RN are proposed) can be broken into two subcategories, interpretative and matching, depending on the nature of the process used to secure the identity. To wit, an interpretative identification is made on the basis of independent and subjective scientific interpretation of data (for example, the infamous accounting for all the peaks in a mass spectrum by drawing structures on a napkin, more rigorously referred to as structure elucidation), whereas a matching identification is made on the basis of objective comparative data such as a mass spectral match to a database. Although either means may be appropriate to secure a tentative identity and likely both means are equally valid, they are quite different means and processes that get to the same point.

In reviewing the criteria for a tentative identification, we understand that it is a one-dimensional outcome; that is, it is an identification based on one item of confirming information. It is intuitive that the more confirming information one has, the greater confidence one has in the identity, and the greater the likelihood that the identification is correct. So, for example, a two-dimensional identification—that is, an identification based on two independent pieces of information—becomes a confident identification. For example, a tentative identification can be secured independently by both means, matching and interpretation. These two pieces of information, independent and confirmatory, together support a more confident identification.

At some point, one can collect so much confirmatory information that they become highly confident that their identification is correct, and it is the case that the chances that the identification is wrong become vanishingly small. For example, a three-dimensional identity (an identity based on three pieces of confirmatory information) is surely an identification in which one has high confidence. In the circumstance of compelling and overwhelming confirmatory information, surely one can envision that the identification has been confirmed by the preponderance of data.

There is also the more traditional understanding of a confirmed identity, that is, a confident identity that has been confirmed by comparison to an authentic reference standard. In this case, comparison to an authentic reference standard can be considered the third dimension of identification. Thus, in Figure 1 there are two flavors of a confirmed identity: data-based (preponderance of data) and standard-based (authentic reference standard).

These identification categories establish an identification hierarchy consisting of the five categories, as listed in Figure 1.

Although it is fine to have established a hierarchy, it is infinitely more useful to have established the criteria upon which placement in the hierarchy is based. To this end, a hierarchy has been established in Table I for a specific analyte, ultimately established to be di-(2-ethylhexyl) phthalate. Based on the available information, the identification of this analyte is tracked from unidentified to confirmed as more and different information is obtained. A similar example, considering the identification of a butyl rubber oligomer, is contained in the reference by Christiaens et al. (4).

A useful means of understanding the utility of the proposed classification is to compare it with the existing classification proposed by PQRI and USP. The fit of the five classification categories in Table I and Figure 1 with the four categories in USP <1663> is established in Table II. It is concluded that the identification hierarchy discussed herein is consistent with, and an embellishment of, the USP <1663> identification categories.

In reviewing the hierarchy, one notes the terms interpretative and matching occupy the same position in the hierarchy [tentative, the lowest position (least amount of information) for which one is able to make an “educated guess” at the compound’s specific identity]. These two classes differ not necessarily in terms of the information from which the identity is deduced but rather by the means by which the identity is deduced. For example, consider a compound revealed by GC/MS with its associated mass spectrum. If the mass spectrum is interpreted by an expert to elucidate the compound’s identity, then the identity is the result of an interpretative process. However, if the mass spectrum is matched to a mass spectral database, then the inferred identity is the result of a matching process.

Similarly, one notes that the terms data-based and standard-based occupy the same position in the
The identification hierarchy, which establishes identification categories. As the amount and rigor of confirming information increase, the information content of the identity increases and the likelihood that the identity is correct increases.

An important question concerning the use of identities in compatibility assessment frequently comes up, although it is phrased in different ways. This question is “what level of identification is required so that the identification can be a solid basis for a rigorous and proper impact assessment?”

An extractable’s identity is typically used to infer or assess the effect of that extractable, typically, but not solely, its safety impact. As an identification of “unidentified” has no significance except that an extractable has been discovered at a level above a relevant threshold, clearly an unidentified compound cannot be assessed, in terms of suitability for use impacts, in a direct manner. Alternatively, confident and confirmed identities can be assessed for their potential suitability impact directly, as the degree of confidence in the identity is sufficiently high that it is likely the assessment will be proper and rigorous and the information content of the identity is sufficiently high that relevant compatibility information can be found (assuming that it exists).

A partial identification provides structural information but not a specific identity. Thus, a partial identification cannot be rigorously assessed in the same manner as a higher-level identification. However, a partial identity can be assessed by means that are structure driven, for example, in silico means of inferring general safety, carcinogenicity, and mutagenicity. The value of the partial identity is that in silico assessment may influence the determination of the reporting threshold for extractables or leachables. Specifically, the analytical evaluation threshold (AET) is used as a means of establishing which extractables or leachables must be reported for safety assessment (5). If the in silico assessment of a partially identified extractable indicates that it has no structural alerts for mutagenicity,
<table>
<thead>
<tr>
<th>Information Content</th>
<th>Information Type</th>
<th>Information Example</th>
<th>Title</th>
<th>Reporting Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insufficient ...</td>
<td>Chromatographic and/ or spectroscopic data that provide little or no insight into the possible structure or identity</td>
<td>1. GC/FID peak with no GC/MS peak. 2. GC/MS peak with no library hits and uninterpretable spectra. 3. LC/UV peak with no MS signal. 4. LC/MS peak with uninterpretable spectra.</td>
<td>Unidentified</td>
<td>Unidentified</td>
</tr>
<tr>
<td>Sufficient information to propose a structure but insufficient information to propose a specific identity</td>
<td>Chromatographic and/or spectroscopic data that are sufficient to infer a general structure but not sufficient to propose a specific identity</td>
<td>1. Peak with GC/MS or LC/MS spectrum that can be interpreted sufficiently that a structure can be inferred. 2. Structure is inferred by reference to internal/external literature. 3. Accurate mass MS that infers the empirical formula only.</td>
<td>Partial</td>
<td>A phthalate (e.g., di-(2-ethylhexyl) phthalate)</td>
</tr>
<tr>
<td>Sufficient information to propose a specific identity</td>
<td>Chromatographic and/or spectroscopic data that are sufficient to infer a specific identity; however, additional data do not exist to support the identity (one dimension)</td>
<td>One-dimensional information that is one of the following: 1. GC/MS peak with library spectral match. 2. LC/MS peak with definitive molecular weight and match to an equivalent molecular weight in a GC/MS peak. 3. GC/MS or LC/MS peak whose structure has been elucidated by expert interpretation of the mass spectrum.</td>
<td>Tentative (interpretative or matching)</td>
<td>Di-(2-ethylhexyl) phthalate, tentative</td>
</tr>
<tr>
<td>Sufficient information to support a proposed specific identity</td>
<td>Chromatographic and/or spectroscopic data that are sufficient to infer a specific identity; inference is supported by additional data (two dimensions).</td>
<td>Two-dimensional information that includes the following pairs: 1. GC/MS peak with library spectral match or LC/MS peak with definitive molecular weight and match to an equivalent molecular weight in a GC/MS plus retention time match. 2. GC/MS peak with library spectral match or LC/MS peak with definitive molecular weight and match to an equivalent molecular weight in a GC/MS plus accurate mass.</td>
<td>Confident</td>
<td>Di-(2-ethylhexyl) phthalate, confident</td>
</tr>
<tr>
<td>Information Content</td>
<td>Information Type</td>
<td>Information Example</td>
<td>Title</td>
<td>Reporting Example</td>
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<tr>
<td>3. GC/MS peak with library spectral match or LC/MS peak with definitive molecular weight and match to an equivalent molecular weight in a GC/MS plus MS/MS fragment pattern interpretation.</td>
<td>Chromatographic and/or spectroscopic data that are sufficient to infer a specific identity; inference is supported either by comparison to an authentic reference standard of the inferred substance or a preponderance of supporting data (three or more dimensions).</td>
<td>Retention time and spectral match to an authentic reference standard. Three-dimensional information including three or more collaborating pieces of information (e.g., GC/MS spectral match, LC/MS spectral match, GC/MS and LC/MS accurate mass-provided chemical formulas)</td>
<td>Confirmed (data-based or standard-based)</td>
<td>Di-(2-ethylhexyl) phthalate, confirmed</td>
</tr>
<tr>
<td>4. GC/MS peak with library spectral match or LC/MS peak with definitive molecular weight and match to an equivalent molecular weight via GC/MS plus inference from internal or external literature.</td>
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<tr>
<td>5. GC/MS peak with library spectral match or LC/MS peak with definitive molecular weight and match to an equivalent molecular weight in a GC/MS plus inference from NMR.</td>
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<td>6. The same identity is proposed by orthogonal analytical methods (e.g., both GC/MS plus LC/MS) independently.</td>
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</tbody>
</table>

In this Table, the term “or” refers to two pieces of information, either of which serves, in the absence of the other, as the basis of an identification. The term “plus” means two independent pieces of information which both separately and collaboratively support the same identity. “The type of data required for an identity to fall within a given category is given, and the use of that information to establish an identity is illustrated using an example compound, di-(2-ethylhexyl) phthalate.
<table>
<thead>
<tr>
<th>Level</th>
<th>Information Content</th>
<th>Information Type</th>
<th>Description per USP &lt;1663&gt;</th>
<th>Title in USP &lt;1663&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Insufficient</td>
<td>Chromatographic and/or spectroscopic data that provide little or no insight into the possible structure or identity</td>
<td>Not used in USP &lt;1663&gt; but inferred to be a compound whose identity cannot even be proposed based on the available data.</td>
<td>Unknown</td>
</tr>
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<td></td>
<td>information to</td>
<td></td>
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<tr>
<td></td>
<td>propose a structure</td>
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<tr>
<td></td>
<td>or identity</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>(Unidentified)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>2</td>
<td>Sufficient</td>
<td>Chromatographic and/or spectroscopic data that are sufficient to infer a general structure but not sufficient to propose a specific identity</td>
<td>Data have been collected that are consistent with a class of molecule only. Examples of such data include mass spectrometric fragmentation behavior/expert mass spectrum interpretation and mass spectrum matches automated library or literature spectrum</td>
<td>Tentative</td>
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<td></td>
<td>information to</td>
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<td></td>
<td>propose a structure</td>
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<td></td>
<td>but insufficient</td>
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<td></td>
<td>information to</td>
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<tr>
<td></td>
<td>propose a specific</td>
<td></td>
<td></td>
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<td></td>
<td>identity (Partial)</td>
<td></td>
<td></td>
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<tr>
<td>3</td>
<td>Sufficient</td>
<td>Chromatographic and/or spectroscopic data that are sufficient to infer a specific identity; however, inference is not supported by additional data.</td>
<td>Not used in USP</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>information to</td>
<td></td>
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<tr>
<td></td>
<td>propose a specific</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>identity (Tentative)</td>
<td></td>
<td></td>
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<tr>
<td>4</td>
<td>Sufficient</td>
<td>Chromatographic and/or spectroscopic data that are sufficient to infer a specific identity; inference is supported by additional data.</td>
<td>A tentative identification that has been bolstered by additional and sufficient confirmatory information to preclude all but the most closely related structures. Such confirmatory information could include confirmation of molecular weight, confirmation of elemental composition (via accurate mass), and supporting spectral information from an orthogonal method (e.g., NMR)</td>
<td>Confident</td>
</tr>
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<td></td>
<td>information to</td>
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<td></td>
<td>support a proposed</td>
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<tr>
<td></td>
<td>specific identity</td>
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<td></td>
<td>(Confident)</td>
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<td></td>
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<tr>
<td>5</td>
<td>Sufficient</td>
<td>Chromatographic and/or spectroscopic data that are sufficient to infer a specific identity; inference is supported either by comparison to an authentic reference standard of the inferred substance or via a preponderance of collaborating data.</td>
<td>A preponderance of evidence confirms the entity in question can only be the identification provided. Although it is possible that a highly confident identification may meet the standard implied by the preponderance of evidence, the only means of providing a confirmed identification is via mass spectral and retention time match with an authentic reference compound.</td>
<td>Confirmed</td>
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<td></td>
<td>information to</td>
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<td></td>
<td>confirm a specific</td>
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<tr>
<td></td>
<td>identity (Confirmed)</td>
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then perhaps the calculation of the AET can be based on a more general safety threshold, such as the qualification threshold versus the safety concern threshold or threshold of toxicological concern. Alternatively, if the in silico assessment of a partially identified extractable indicates structural alerts, then perhaps the calculation of the AET must consider and address a safety threshold that is consistent with the alert.

Given its limited information content and its high degree of uncertainty (low degree of confidence), a partial identity should never be the starting point for a rigorous impact assessment.

Mechanistically, a tentative identification can be assessed for suitability for use considerations, as the tentative identification typically assigns a single and specific identity to an extractable or leachable. However, given the level of uncertainty in a tentative identification, it is appropriate to question whether these types of identification are sufficiently robust to be the basis of a rigorous compatibility assessment. Thus, it is prudent to revisit a tentative identification depending on the outcome of the compatibility assessment. If the outcome of the assessment is definitive (either compatible or noncompatible), then the tentative identity is judged to be sufficiently robust to be the basis of the assessment. This is the case as the “margin of error” associated with the identity being tentative is covered by the definitive assessment outcome. However, if the outcome of the suitability for use assessment for a tentatively identified compound is equivocal or borderline, then the identification should be elevated to either confident or confirmed by collecting the required supporting data.

Consider safety assessment, for example. One measure used to support safety assessment is the margin of safety (MoS), which is the ratio of a substance’s tolerable intake (established by the compound’s identity and toxicological safety profile) and the patient’s daily exposure to a substance (established in part by a substance’s concentration). An MoS \( > 1 \) (daily exposure less than the tolerable intake) is generally interpreted as an acceptable outcome, implying that there is a negligible risk that the patient’s health would be adversely affected by the substance. In circumstances when the interpretation of the MoS is definitive (for example, either MoS \( > 10 \) and it is definitely concluded that the patient safety risk is negligible or MoS \( < 0.1 \) and it is definitely concluded that the patient safety risk is possibly considerable), uncertainty in the identity may be irrelevant to the assessment outcome. That is to say that even if the tentative identity were incorrect, likely the true identity is structurally similar to the incorrect initial identity and, thus, that the toxicity of the compound with the true identity is similar to the toxicity of the compound with the incorrect identity. If this is the case, then it is unlikely that the toxicity of the incorrectly and correctly identified compound differ by as much as a factor of 10, and the conclusion of the assessment remains valid.

However, when the MoS based on a tentative identification is between the values of 0.3 and 3 (for example), then the error in the reported identity is sufficiently high that there is little or no margin for error in the assessment. In such cases, the tentative identification is not the proper basis of the safety assessment, and a higher level of identification must be secured so that the safety assessment can become more rigorous and more correct.

Impact assessments can be confidently based on either a confident or a confirmed identity; thus, it should be the goal of the analytical chemist to reach these levels of identification.

Quantitation Classification

Whereas a compound’s identity establishes its “no effect” level, a compound’s concentration is used to establish the patient’s exposure level to the compound. That is, the identity is used to establish the permissible exposure while the concentration establishes the actual exposure. It is often the case that the compatibility assessment simplifies to a comparison of permissible exposure to actual exposure.

As was the case with identification, an analytical method does not produce an analyte’s concentration directly; rather, the method’s response to the analyte is “calibrated” by some means to infer or estimate the analyte’s concentration. As was also the case with identification, there is the ideal situation and then there is the practical reality associated with quantitation. Clearly, the ideal situation of obtaining the most accurate estimate of an analyte’s concentration in a sample is achieved when the test method’s response to the analyte has been calibrated via the generation of a calibration curve obtained by the analysis of multiple standards specific to the analyte and prepared to
contain the analyte at known and relevant concentrations. However, given the large and diverse population of potential extractables and leachables and the circumstance that most extractables’ or leachables’ profiles consist of numerous and largely unpredictable substances, generation of a response curve for each individual extractable (or leachable) is impractical, if not impossible; hence, exact or accurate quantitation is rarely performed during E&L screening. Rather, the analyte’s concentration is estimated by making certain assumptions about its response and response curve, typically in reference to an internal standard.

Recognizing that accuracy of (or inaccuracy in) a concentration estimate depended on the validity of the response assumptions made, the ISO 10993-18 standard for the chemical assessment of medical devices (1) established categories of quantitation, which are summarized as follows (see also Figure 2):

1. Estimated concentration: an analyte’s concentration obtained by using the response from a surrogate substance chosen without specifically addressing or considering the relative responses of the analyte and the surrogate. (Note that in the ISO Standard the actual term used is estimated quantitative concentration).

2. Semiquantitative concentration: an analyte’s concentration obtained by using the response from a surrogate substance (or substances), specifically accounting for the relative responses of the analyte and the surrogate. (Note that in the ISO Standard the actual term used is semiquantitative analysis).

3. Quantitative concentration: an analyte’s concentration obtained by using a response function (calibration curve) generated specifically for the analyte via the use of a reference standard. (Note that in the ISO Standard the actual term used is quantitative analysis).

It should be clear from these definitions that an estimated concentration is generally less accurate and more uncertain than a semiquantitative concentration, which is generally less accurate and more uncertain than a quantitative concentration.

The three quantitation categories are all based on certain simplifying assumptions that may or may not be valid. For example, an estimated concentration is obtained based on the assumptions that (1) the response factor for all analytes is the same as that of the chosen internal standard, and (2) the response factors are unaffected by the absolute and relative concentrations of the analytes and the internal standard. Given the known and potentially large variation in response factors for either GC/MS or LC/MS screening methods (for example, 6–10), clearly the first assumption is more wishful thinking than reality; hence, the use of the term “estimated” to describe this quantitation category. Although this type of quantitation may have been referred to (incorrectly) as “semiquantitative” by practitioners of the art, the term semiquantitative implies a level of rigor and a degree of confidence that is not justified considering the means by which the estimated concentration is obtained.

The second category, semiquantitative, takes care of the first concern because semiquantitation is based on an analyte-specific relative response factor, determined
by the analysis of a standard solution containing the compound of interest and the internal standard at known (and typically equal) concentrations. However, the accuracy of semiquantitative concentrations could be adversely affected by concentration differences (mismatches) between the analyte of interest and the internal standard and the analyte in the sample versus the analyte in the standard.

The third category, quantitation, takes care of both concerns with respect to response variations across analytes and across concentrations, as the reported concentration is based on each analyte’s unique response function (calibration curve). It is noted that quantitative is a requirement for, and is most easily achieved in, target analysis.

As was the case with the identification hierarchy, it is relevant to consider what level of quantitation is necessary to support rigorous impact assessment. On the surface, it is reasonable that one would conclude that an estimated concentration is never appropriate as the basis of a rigorous impact assessment. However, the validity of this statement depends somewhat on the outcome of the assessment. As was done previously for identification, consider safety assessment and the MoS as an example. In circumstances when the interpretation of the MoS is definitive (for example, either MoS > 10 and it is definitely concluded that the patient safety risk is negligible or MoS < 0.1 and it is definitely concluded that the patient safety risk is possibly considerable), uncertainty in the estimated concentration may be irrelevant to the assessment outcome. For example, consider the case in which the error in the estimated concentration is sufficiently large that its estimated concentration is a factor of 5 less than its true concentration. In the case of the MoS > 10, an MoS adjusted for the error would still be MoS > 2, which would still support the conclusion of negligible safety risk. In the case of the MoS < 0.1, an MoS adjusted for the error would still be MoS < 0.1, which would still support the conclusion of considerable safety risk. Thus, in these cases, an estimated concentration could be an adequate basis of the toxicological safety risk assessment.

However, when the MoS based on an estimated concentration is between the values of 0.3 and 3 (for example), then the error in the estimated concentration is sufficiently high that there is little or no margin for error in the assessment. In such cases, the estimated concentration is not the proper basis of the safety assessment. However, in these cases, an estimated concentration becomes the basis of a screening decision to secure a more accurate quantitation to serve as the basis of the assessment.

Semiquantitative and quantitative concentrations, given their higher certainty and greater confidence, are both suitable starting points for impact assessment. It is unclear to this author whether the increased certainty and confidence in quantitative concentrations is necessary, especially considering the practical difficulties associated with securing such information. Nevertheless, if quantitative concentrations can be obtained, then they should be the basis of the impact assessment.

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Conflict of Interest Declaration

The author declares that he has no competing or conflicting interests.

References


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