Development of Safety Qualification Thresholds and Their Use in Orally Inhaled and Nasal Drug Product Evaluation

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Submitted to Toxicological Sciences for consideration as a Review article

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Abstract

Safety thresholds for chemical impurities and leachables in consumer products such as foods and drugs have helped to ensure public health while establishing scientifically sound limits for identification and risk assessment of these compounds. The Product Quality Research Institute (PQRI) Leachables and Extractables Working Group, a collaboration of chemists and toxicologists from FDA, industry, and academia, has developed safety thresholds for leachables and extractables in orally inhaled and nasal drug products (OINDP), for application in United States pharmaceutical submissions. The PQRI safety concern threshold (SCT) is 0.15 µg/day, and the qualification threshold (QT), 5 µg/day. OINDP are important in the treatment of lung diseases such as asthma and chronic bronchitis, as well as systemic diseases such as diabetes. Analysis of extractables and minimization of leachables in OINDP are vital to ensuring the quality and safety of the final product. It is expected that the thresholds developed by the PQRI Leachables and Extractables Working Group will be used by both industry and regulators to ensure and assess such quality and safety in OINDP applications. In this paper, we describe the importance of the PQRI safety thresholds in the OINDP pharmaceutical development process; the background and context of safety thresholds for consumer products; how these safety thresholds were developed using well-established, robust databases and quantitative risk assessment approaches; and how these thresholds can be applied in a pharmaceutical safety qualification process, including FDA regulatory perspectives on the use of safety thresholds for OINDP.

Keywords: qualification threshold, safety concern threshold, leachables, extractables, inhalation, nasal, PQRI
I. Introduction

A. Why are extractables and leachables important in inhalation drug product pharmaceutical development?

Extractables, as defined by the U.S. Food and Drug Administration (FDA), are compounds that can be extracted from elastomeric components, plastic components, or coatings of the container and closure system when in the presence of an appropriate solvent(s).

Leachables are compounds that leach from elastomeric or plastic components or coatings of the container and closure system as a result of direct contact with the drug product formulation (Food and Drug Administration, 1998 and July 2002). Extractables are therefore potential leachables, and patients could be exposed to leachables. Leachables in orally inhaled and nasal drug products (OINDP) are generally considered by pharmaceutical regulatory agencies to be of significant safety concern (FDA, 1999) because for some OINDP, leachables could be delivered directly to the diseased lung. For OINDP, toxicological and chemical assessments of leachables and extractables are a critical part of the pharmaceutical development process. Further, extractables and leachables can often impact on the marketing approval of a drug product.

OINDP include nasal sprays and inhalation sprays, metered dose inhaler (MDI) solutions and suspensions, inhalation solutions, and dry powder inhalers (DPIs). These drug products are used to mitigate the effects of indications such as asthma, emphysema, and allergy symptoms, and to deliver medication directly to affected areas such as the nasal passages and lungs (local delivery). Newer inhalation products, such as those for delivery of insulin to treat diabetes, seek to deliver medication throughout the body, via the lungs (systemic delivery).

Each inhalation or nasal drug product, includes a container closure system that is a vital part of the drug product as a whole, facilitating drug delivery and protecting the integrity of the
formulation. For example, the MDI consists of a solution or suspension formulation (drug substance or active pharmaceutical ingredient; chlorofluorocarbon (CFC) or hydrofluoroalkane (HFA) propellants to facilitate aerosol dose delivery; and surfactants, co-solvents and other excipients to help stabilize the formulation), and a container closure system with various physical components (metal canister to contain the pressurized formulation; a valve to meter the formulation dose to the patient; elastomer components to seal the valve to the can and contain the pressurized formulation; and an actuator/mouthpiece to facilitate patient self-dosing). The formulation and container closure system are closely integrated in the MDI drug product, which is generally true of all OINDP. The container closure systems for OINDP from which leachables may appear can include not only primary packaging components, e.g., canisters for MDIs and blister packages for DPIs, but also secondary packaging, such as overwraps or labels that are not in direct contact with the drug formulation.

OINDP container closure systems components can consist of various elastomeric (rubber) and polymeric (plastic) materials. These components can be seals, parts of MDI valves, mouthpieces, etc. All such elastomeric and polymeric materials contain relatively low molecular weight soluble organic chemical entities, either purposefully added to the materials during synthesis, compounding, or fabrication (e.g., polymerization agents, fillers, antioxidants, stabilizers, and processing aids), or present in the materials as a by-product of synthesis, compounding, or fabrication (e.g., oligomers, additive contaminants, and reaction products). All of these chemical entities have the capacity to leach into the formulation and be delivered to the patient. Leachables and extractables represent a variety of chemical types and classes, and leachables can be present in inhalation drug products at widely varying concentrations. Extractables and leachables can also include certain structure types with known safety
implications, such as N-nitrosamines, polyaromatic hydrocarbons (PAHs), and mercaptobenzothiazoles (FDA, November 1998 and July 2002).

B. Why do we need safety thresholds?

Modern analytical chemistry has enormous capability for analyzing extractables and leachables. For example, Gas Chromatography/Mass Spectrometry (GC/MS) and Liquid Chromatography/Mass Spectrometry (LC/MS), are capable of separating, identifying and quantifying highly complex mixtures of organic chemical entities such as those produced from Controlled Extraction Studies of OINDP container closure system components (see Figure 1) (Norwood et al., 2005). These analyses are routinely accomplished at very high sensitivity, easily detecting organic leachables at low µg/canister levels in MDIs (Norwood et al., 1995).

The available scientific literature would indicate that many hundreds, if not thousands, of individual chemical entities that can appear as extractables/leachables could potentially be detected, identified, and quantified at similar levels.

However, it is well established that there are levels at or below which organic chemical entities in drug product represent no safety concern to patients. Therefore, the establishment of safety thresholds that are protective of patients for OINDP leachables and extractables can be justified and are believed to be necessary to limit unreasonable and extended evaluations of chemicals present at levels that cannot harm patients. An efficient pharmaceutical development process requires guidance on “how low to go” for the identification and quantification of extractables and leachables.
Figure 1. A GC/MS extractables “profile” of an elastomer (Total Ion Chromatogram of a solvent extract).
To ensure quality and safety of OINDP through knowledge of amounts and types of extractables and leachables, safety thresholds must be applied in conjunction with pharmaceutical development “best practices,” which include safety assessment of potential leachables throughout the development program. Such assessment should include at a minimum:

- safety evaluation of supplier information during container closure component selection;
- safety evaluation of potential leachables during Controlled Extraction Studies on OINDP components;
- safety evaluation of leachables;
- and safety input to extractables specifications for routine quality control of extractables.

**C. The PQRI Leachables and Extractables Effort**

In 2001, the Product Quality Research Institute (PQRI) initiated a project to develop safety and analytical thresholds for leachables and extractables in OINDP. At the time there was no regulatory guidance available for such thresholds. Furthermore, International Conference on Harmonisation (ICH) thresholds for impurities are not applicable to leachables and extractables in OINDP (ICH Q3A(R1), 2003; ICH Q3B(R2), 2003; ICH Q3C(R3), 2003).

The PQRI Leachables and Extractables Working Group, consisting of toxicologists and chemists from industry, FDA, and academia, developed a safety concern threshold and a qualification threshold for leachables; an analytical evaluation threshold for extractables and leachables; processes for applying these thresholds; and best practices for selecting OINDP container closure system components and conducting Controlled Extraction Studies, leachables studies, and routine extractables testing.

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1 Product Quality Research Institute: [http://www.pqri.org](http://www.pqri.org)
The PQRI safety concern threshold (SCT) is proposed to be 0.15 µg/day, and the qualification threshold (QT), 5 µg/day. The SCT is the threshold below which a leachable would have a dose so low as to present negligible safety concerns from carcinogenic and noncarcinogenic toxic effects. The QT is the threshold below which a given non-carcinogenic leachable is not considered for safety qualification (toxicological assessments) unless the leachable presents structure-activity relationship (SAR) concerns. Below the SCT identification of leachables generally would not be necessary. Below the QT leachables without structural alerts for carcinogenicity or irritation would not require compound-specific risk assessment.

In 2006, the PQRI recommendations were submitted to the FDA for consideration in the FDA’s development of regulatory recommendations for OINDP (PQRI, 2006). Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products. http://www.pqri.org). This paper describes, from a United States perspective, historical background on the development and application of safety thresholds for consumer products; the development and application of the PQRI safety thresholds for leachables in OINDP; and FDA regulatory perspectives on the use of these safety thresholds.

I. Concept and History of Safety Thresholds

Over five hundred years ago Paracelsus made the astute observation that: “All substances are poisons; there is none which is not a poison. The right dose differentiates a poison from a remedy.” A corollary to this bit of wisdom is that for most or perhaps even all toxicological effects, there exist thresholds: a dose below which an exposure imparts no risk. While most toxicologists would likely agree with this principle, the means for calculating the threshold can sometimes be controversial. In addition, for some adverse health endpoints, i.e., mutagenesis and carcinogenesis, most regulatory agencies have assumed a lack of a threshold. Practically,
this means that any exposure results in some increased risk for mutation and/or cancer.

Nevertheless, it is often impossible to reduce human exposures to zero.

Two types of methodologies have evolved in risk assessment: one for calculating safe exposure values for health effects thought to have thresholds, and a second for calculating “virtually safe” exposure values for health effects thought to lack thresholds. In both cases, the method involves extrapolation of agent-induced health effects in animals to human risk. For drug development, methodologies for threshold-associated exposures are discussed in ICH Q3C, Impurities: Guideline for Residual Solvents (ICH Q3C(R3), 2003). The guideline discusses a method for calculating a PDE, “permissible daily exposure” to a residual solvent. Calculating PDEs for mutagenic and carcinogenic substances is more complex. In this case, a “virtually safe dose” can be established, using animal studies, as a dose that implies a negligible risk when administered over a lifetime. A virtually safe dose has been defined somewhat differently by different regulatory agencies. In general, however, it refers to lifetime exposures that increase the risk of cancer by either one in one million or one in one hundred thousand.

These types of risk assessments are often used to calculate acceptable levels of carcinogens in drinking water, air, and soil at hazardous waste sites. In order to perform such risk assessments, data from rodent lifetime bioassays are required. Data from such studies are often not available for impurities found in drug substances and drug products, and because of the resource intensity and protracted nature of rodent lifetime bioassays, it is generally not practical to test all potentially carcinogenic impurities in such an assay. This conundrum has led toxicologists to devise the concept of the “threshold of toxicological concern” (TTC) (Kroes, et al., 2004). These authors define the TTC as “a level of exposure for all chemicals, whether or not there are chemical-specific toxicity data, below which there would be no appreciable risk to
human health.” The concept of a TTC appears to have originated with FDA’s threshold of regulation for indirect food additives (FDA, 1995).

In general, an impurity exposure level of 1.5 µg/person/day is considered an acceptable threshold below which further qualification for genotoxicity/carcinogenicity concerns would not be required. The qualification threshold was originally developed as a “threshold of regulation” by the Center for Food Safety and Applied Nutrition (CFSAN) at the FDA for food contact substances and was further standardized by the CFSAN/FDA in a companion guidance document for food contact substances (FDA, 1995 and April 2002). Substances with no known cause for concern that may migrate into food are exempted from regulation as a food additive if present at daily dietary concentrations at or below 0.5 parts per billion, corresponding to 1.5 µg/person/day based on a total daily consumption of 3 kg of solid and liquid foods. The threshold is an estimate of daily exposure expected to result in an upper bound lifetime risk of cancer of less than 10⁻⁶, considered a “virtually safe dose”. The initial CFSAN/FDA analysis was based on an assessment of 343 carcinogens from a Carcinogenic Potency Database (CPDB) and was derived from the probability distribution of carcinogenic potencies of those compounds (FDA, 1995; Gold et al., 1984; Rulis, 1992). Subsequent analyses of an expanded database of more than 700 carcinogens further confirmed the threshold (Fiori and Meyerhoff, 2002). Additional analysis of subsets of highly potent carcinogens suggested that a threshold of 0.15 µg/day, corresponding to a 10⁻⁶ lifetime risk of cancer, may be more appropriate for chemicals with structural alerts for potential genotoxicity (Kroes et al., 2004). Some structural groups including aflatoxin-like-, N-nitroso-, and azoxy-compounds were identified to be of extremely high potency and are excluded from the threshold approach.
United States federal regulatory agencies such as the EPA and FDA typically use a $10^{-6}$ lifetime risk of cancer to determine “acceptable” risk from chemical exposures, although higher risk levels are accepted under certain circumstances, namely for active pharmaceutical ingredients from which a benefit may be derived. This level of exposure is expected to produce a negligible increase in carcinogenic risk based on the analysis of the CPDB. Additionally, this threshold is considered to be low enough to ensure that the presence of an unstudied compound that is below the threshold will not significantly alter the risk/benefit ratio of a drug product, even if the impurity is later shown to be a carcinogen.

In developing the SCT and QT, the PQRI Working Group carefully considered the assumptions, approaches and, where possible, exposure data used in developing the threshold of regulation for food additives, the TTC, and ICH thresholds for impurities. The Working Group took a relatively conservative approach in the assumptions applied to development of the SCT and QT. These assumptions were in many cases different than those used in development of these other thresholds, taking into account the possibility of mixtures of leachables, and a real potential for the presence of carcinogenic leachables. Further, unlike impurities, which are associated with drug substance or drug product, leachables are not drug related and could possess different toxic characteristics. The approaches to and assumptions made in establishing the SCT and QT are explained below.

III. Safety Thresholds for Leachables in OINDP

Because leachables originate in the container closure system rather than the synthetic pathway, the PQRI SCT and QT are based solely on µg/day intake of leachables, unlike ICH thresholds for drug product impurities, which are linked to the dose of the active pharmaceutical ingredient. The PQRI thresholds were defined in relation to estimated safe human inhalation
exposures for sets of chemicals assessed for different toxicity endpoints, an approach similar to
that used by others to determine thresholds for orally ingested substances (Blackburn et al.,
2005; Cheeseman et al., 1999; Dolan et al., 2005; Fiori and Meyerhoff, 2002; Kroes et al., 2000;
Kroes et al., 2004; FDA, 1995; Munro et al., 1996; Rulis, 1992).

A. Derivation of the Safety Concern Threshold (SCT)

The SCT is based on carcinogenicity endpoints because carcinogenic effects occur at
lower intakes than those associated with noncarcinogenic toxicity. This was previously
demonstrated for orally ingested compounds, including those with potent neural, reproductive, or
endocrine toxicity (Kroes et al., 2000). Our analysis confirms that genotoxic carcinogenicity is a
concern at lower doses of inhaled compounds than acute respiratory irritation, or chronic
respiratory and systemic toxicity.

The Working Group based the SCT on the potencies of genotoxic carcinogens (i.e,
positive for mutations in Salmonella, SAL+) in the Carcinogenic Potency Database (CPDB),
which expresses carcinogenic potency as the TD50, the daily dose inducing a particular tumor
type in half of the animals that otherwise would not develop the tumor over a lifetime. Human
$10^{-6}$ risk specific doses were estimated by linear extrapolation from the TD50 (Blackburn et al.,
2005; Cheeseman et al., 1999; Fiori et al., 2002; Krewski et al., 1990; Kroes et al., 2004; Rulis,
1992). As expected (Cheesman et al., 1999), SAL+ carcinogens are more potent carcinogens
(Figure 2). The SAL+ compounds are also appropriate for establishing a threshold for structural
identification because structural alerts are more predictive for SAL+ than for nongenotoxic
carcinogens (Benigni and Zito, 2004). Furthermore, most known human carcinogens are
genotoxic (Bartsch and Malaveille, 1989), and the assumption of linear extrapolation of cancer
risk is more appropriate for SAL+ compounds than for nongenotoxic compounds, which may
exhibit mechanism-based thresholds for tumorigenesis. Too few inhalation studies were
represented in the CPDB to establish a threshold based solely on inhalation data. However, the
potency of carcinogens tested by inhalation mirrors that of those tested by all routes (Figure 2);
thus data from all routes should be representative of inhalation carcinogens.

A $10^{-6}$ risk specific dose was used as a negligible carcinogenicity risk in our analysis,
consistent with the threshold of regulation for indirect food additives (FDA, 1995). The
relatively conservative $10^{-6}$ risk level was considered an appropriate starting point for
identification and evaluation of leachable impurities because it is not uncommon for there to be a
mixture of multiple leachable impurities with potential genotoxicity issues in an OINDP, and
there are examples of potent carcinogens found as leachables in OINDP.

Our estimates of human $10^{-6}$ risk specific doses included allometric scaling factors, based
on default body weights (70-kg human, 350-g rat, 30-g mouse) to the 0.75 power, used by the
U.S. Environmental Protection Agency (EPA, 1992). In U.S. pharmaceutical labeling, dose
metrics from carcinogenicity assays are typically scaled to body surface area on a mg/m$^2$ basis
(default body weight to the 2/3 power). These two specific dose-scaling approaches result in
relatively small (<2-fold) differences in human dose estimates (FDA, 2005), considering that
carcinogen potencies range over several orders of magnitude. Because applying multiple
conservative assumptions can unrealistically overestimate carcinogenic risk (Gaylor et al., 1993),
the Working Group used a central estimate of risk rather than an upper-bound 95% risk estimate,
and used the geometric mean of potencies from rats and mice rather than using the most sensitive
species. Based on these assumptions, the median human equivalent $10^{-6}$ risk specific dose for
SAL+ carcinogens in the CPDB is 0.36 µg/day, and the median excess cancer risk at the SCT of
0.15 µg/day is $0.41 \times 10^{-6}$. If <20% of random chemicals are genotoxic carcinogens (Fung et al.,
1995; Sawatari et al., 2001), <7% of all compounds would exceed $10^{-6}$ increased cancer risk at lifetime intakes <0.15 µg/day. Thus, a leachable below the SCT is unlikely to have a lifetime excess cancer risk >$10^{-6}$, and identification of leachables below this threshold generally would not be necessary.

**Figure 2.** Carcinogenic potency of genotoxic (SAL-positive) and non-genotoxic (SAL-negative) carcinogens from the Carcinogenic Potency Data Base (CPDB) from studies conducted in rodents by inhalation or all routes combined.

**B. Derivation of the Qualification Threshold**

The Qualification Threshold is based primarily on regulatory agency "reference doses" derived by applying safety factors to no-observed-adverse-effect levels (NOAELs) for noncarcinogenic toxicity. The Working Group analyzed 150 inhaled compounds with "Chronic Reference Doses"(RfDs) established by the US EPA, "Minimum Risk Levels" (MRLs)
established by the US Agency for Toxic Substances and Disease Registry, or "Reference Exposure Levels" (RELs) established by the California EPA. The median reference values were: 120 µg/day (10th percentile = 1.5 µg/day) for chemicals with reference values based on respiratory toxicity, and 1940 µg/day (10th percentile = 5.0 µg/day) for chemicals with systemic toxicity endpoints. Based on the large safety margins (~100-fold) incorporated in reference doses, leachables at intakes <5 µg/day should pose negligible health risks. Compounds with respiratory toxicity and inhalation reference values less than 5 µg/day are dominated by metals and metal salts, and by reactive compounds with readily identifiable structural alerts for irritant potential, such as aldehydes and isocyanates.

In developing the QT, the Working Group focused on the total inhaled dose, which assumes 100% deposition, rather than on the actual dose deposited in the lungs. The 5 µg/day QT therefore represents a small percentage - between only 1% and 6% - of the quantity of particulate that individuals are normally inhaling. Note that these percentages would be even smaller if comparison were made to, for instance, air concentrations equal to the National Ambient Air Quality Standard for the respirable fraction (PM$_{10}$), which is considered protective of public health including sensitive sub-populations.

The Working Group also considered acute respiratory irritation in relation to the Qualification Threshold, since potential airway irritation and bronchoconstriction are concerns for impurities in OINDP (Shaheen et al., 1994). A useful metric of sensory irritation is the RD50, the concentration of an irritant that decreases respiratory frequency by 50% in mice (Alarie et al., 1980). A good correlation was reported between occupational threshold limit values and the value of 0.03 × RD50 (Schaper, 1993). To estimate safe doses for respiratory irritants, the Working Group calculated the µg dose at the RD50 concentration inhaled for
10 minutes divided by 1000 for a large set of chemicals (Schaper, 1993). The additional 30-fold safety margin for this metric, compared to the value of 0.03 x RD50, should be sufficient to account for sensitive populations such as asthmatics as illustrated in Table 1. The distribution of RD50/1000 doses was quite similar to the distribution of NOAELs for chronic respiratory toxicity. As with the chronic respiratory toxicants, compounds with RD50/1000 values below the 5 µg/day were predictably irritant compounds such as aldehydes, isocyanates, and nitriles.

Pediatric populations were also considered. Children would be adequately protected by the proposed QT since it is based upon inhalation references values that are intended to protect essentially all people, including sensitive subpopulations such as children. When establishing RfD and RfC values, the EPA identifies the NOEAL, lowest-observed-adverse-effect-level (LOAEL), or benchmark dose or concentration and then divides this value by a series of uncertainty factors, One uncertainty factor relevant to children accounts for variability in toxic response among people, including highly sensitive subjects, such as children and elderly. This intraspecies uncertainty factor usually has a value of 10. This factor can be equally divided into a toxicokinetic variability component with a default value of 3.16 \( [i.e., (10)^{1/2}] \), and a toxicodynamic variability component also with a default value of 3.16, assuming these components act independently.

The intraspecies uncertainty factor of 10 and the associated subfactors of 3.16 have been justified for children based upon multiple studies that have compared the clinical response to pharmaceutical agents in children versus adults as well as the toxic response to chemical agents in younger versus older animals.\( \text{(Burin, 1999; Dourson, 2002)} \) For example, the National Academy of Sciences Committee on Pesticides in the Diets of Infants and Children reviewed several human and animal studies and concluded that the 10-fold intraspecies uncertainty factor...
was sufficient to protect infants and children (Bruckner, 2000). Furthermore, comparison of the
toxicokinetic data of 60 xenobiotics and the toxicodynamic data of 49 xenobiotics in adults,
children, and other groups has shown the composite 10-fold factor covers the great majority of
the population (Renwick, 1998). Further work is needed to determine whether the default
uncertainty factors offer adequate protection for children, especially for inhaled exposure to
gases and particles, and for children with lung disease, such as asthma or cystic fibrosis

The preponderance of current data indicate that a leachable below the Qualification
Threshold is unlikely to cause acute or chronic noncarcinogenic toxicity, and in the absence of
structural alerts for carcinogenicity or irritation should not require compound-specific risk
assessment.

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<th>Table 1. Bronchoconstrictor Concentrations in Asthmatics Relative to Occupational Short Term Exposure Limits (STELs) and RD50 Values</th>
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<td><strong>Compound</strong></td>
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<td>Toluene Diisocyanate</td>
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STEL = Short term exposure limit; RD50 = Concentration decreasing respiratory rate by 50% in mice; NA = Not available.
IV. Application of Safety Thresholds in the Pharmaceutical Development Process for OINDP

In general, the use of safety thresholds is considered acceptable in cases where adequate supporting data are available; the Division of Pulmonary and Allergy Products (DPAP) in FDA’s Center for Drug Evaluation and Research/Office of New Drugs has incorporated the application of safety thresholds in the qualification process conducted for leachables and extractables in OINDP over the last decade. It is recognized that the appropriate application of safety thresholds has advantages, including a reduction in the unnecessary expenditure of animals, time, effort, and money. This reduced expenditure may allow greater resources to be applied to drug development areas that present more significant safety concerns.

Currently, no formal regulatory guidance on the safety evaluation of leachables and extractables is available. In the absence of formal guidance, the DPAP developed an internal practice which includes the following general approach: identification of the compound, determination of the maximum daily human exposure based upon the proposed product specification (e.g., amount of specific leachable in drug product, typically in units of ppm or μg/canister), conduct of a structure activity relationship (SAR) assessment for genotoxic/carcinogenic potential through use of published lists (Ashby et al., 1989; Tennant and Ashby, 1991) or software programs such as DEREK (Deductive Estimation of Risk from Existing Knowledge, www.chem.leeds.ac.uk/luk/) or Multicase (www.multicase.com), and review of available toxicology/safety data bases or conduct of toxicology studies as deemed necessary, e.g., 14-90 day general toxicology, genetic toxicology. The final safety assessment
should be based on a consideration of the maximum expected daily human exposure, the intended patient population, and the anticipated duration of use.

Specific considerations for the safety assessment of leachables and extractables in OINDP include three primary components: systemic toxicity, local toxicity of the respiratory tree, and mutagenic/carcinogenic potential. The DPAP identified a safety threshold for systemic and local toxicity parameters based on an evaluation of the US EPA’s IRIS and HEAST databases (Risk Assessment Information System, Chemical Specific Toxicity Values. Database contains information taken from the United States Environmental Protection Agency’s (EPA’s) Integrated Risk Information System (IRIS), the Health Effects Assessment Summary Tables (HEAST). [www.risk.lsd.ornl.gov/tox/tox_values.shtml](http://www.risk.lsd.ornl.gov/tox/tox_values.shtml) and concluded that there is no significant safety concern for inhaled chemicals with a maximum expected daily dose of 5 µg/day (100 ng/kg) or less. Therefore, no further toxicity data are needed in most cases when the maximum expected daily human exposure is below the stated threshold.

The safety threshold for systemic toxicity was derived from an evaluation of 36 chemicals listed in the EPA database that were administered via the inhalation route and were associated with systemic toxicity. The presumed safe dose derived from the reference concentrations (RfC’s) for these compounds were all ≥ 100 ng/kg with three exceptions; the three exceptions had a “safe” dose of 80 ng/kg. Considering the large safety factors (1,000 – 10,000) that are incorporated into the calculation of RfCs, a safety threshold of 100 ng/kg was considered reasonable. The safety threshold for respiratory toxicity was derived from an evaluation of 20 chemicals with inhalation data that produced respiratory tract toxicity. All but 4 of these chemicals had presumed safe daily inhalation exposures greater than 100 ng/kg based on the RfCs, even after incorporation of large safety factors (300-1,000). Of note, all of the
compounds with a presumed safe dose less than 100 ng/kg had a structural alert associated with respiratory irritation. These structural alerts include isocyanates, aldehydes, organic acids, strained heterocyclic rings, and halogenated aromatic rings.

As described earlier, subsequent data analyses conducted by the PQRI Working Group expanded the database evaluation to include the ATSDR and CAL EPA databases. The Working Group also concluded that a threshold of 5 µg/day presented a negligible safety concern for non-carcinogenic effects, and recommended a qualification threshold of 5 µg/day (100 ng/kg/day, 50 kg person). Thus, the threshold recommended by the Working Group is in agreement with current DPAP practice.

There are some exceptions to the use of the above described threshold approach for leachables and extractables in inhalation products, and these include compounds identified as respiratory irritants and sensitizers, and those that present a known or suspected genotoxic or carcinogenic potential. With regard to respiratory irritants and sensitizers, chemicals should be evaluated for structural alerts associated with irritation or sensitization. This determination is especially important when considering the indicated population for a given product. Most inhalation products approved to date are indicated for treatment of pulmonary diseases such as asthma. These patients are already considered to have a compromised respiratory function and may be more sensitive to the effects of irritants or sensitizers. If a compound is considered to have an irritant or sensitizing potential, patient risk should be assessed on a case-by-case basis after evaluating the available information for the specific compound. Additionally, the clinical experience with the drug product should be evaluated for evidence of any adverse effects. If no concern is identified for irritancy or sensitization, the safety qualification threshold for systemic and local toxicity of 5 µg/day is appropriate. For anticipated clinical exposures greater than 5
µg/day, safety qualification should be conducted for systemic and local toxicity, as described later in this section.

The DPAP currently has no formal policy or practice with regard to a safety threshold for leachables or extractables with an identified or suspected genotoxic or carcinogenic potential. As discussed earlier, the PQRI Working Group proposed a SCT of 0.15 µg/day, a threshold derived from calculated risk-specific doses of genotoxic (SAL-positive) carcinogens from the CPDB and considered to be a dose below which a leachable would present negligible concern for adverse carcinogenic and noncarcinogenic effects. The proposed SCT for negligible carcinogenic effects expands on the DPAP’s previous use of thresholds that focused primarily on general toxicological effects. The PQRI proposal is, however, similar to that described previously by FDA’s Center for Food Safety and Nutrition for the safety assessment of food contact materials (FDA, 2002), and a similar proposal has been made to support safety thresholds for genotoxic impurities (Müller et al., 2006). The proposed approach is supported by a large database, and the applied cancer risk of 10^{-6} is considered appropriate due to the nature of the chemicals that are commonly encountered as leachables and to the lack of any benefit derived from their presence. Notably, high potency carcinogens (e.g., nitrosamines, PAHs) are excluded from this threshold approach. While the PQRI Working Group recommendation has not yet been formally accepted by the FDA, the proposal is considered in DPAP’s safety evaluation of suspected or known carcinogenic leachables and extractables.

Leachables and extractables are considered adequately qualified for genotoxic or carcinogenic potential if they are demonstrated to produce negative results in genotoxicity and/or carcinogenicity assays or, in cases where these data are not available, if they lack structural alerts for these endpoints. When no concern for genotoxic or carcinogenic potential is identified, a
qualification threshold of 5 µg/day is appropriate in the absence of supporting general toxicology data and an identified potential for respiratory irritation or sensitization. If a leachable or extractable is a known or suspected genotoxin or carcinogen, appropriate tests should be conducted or a rationale provided to alleviate this concern. Alternatively, consideration should be given towards reducing the drug product specification to a level associated with the PQRI Working Group recommended SCT of 0.15 µg/day. If the compound is a known carcinogen, the product specification should be set to a level associated with a cancer risk of less than or equal to 10^{-6}.

In general, when adequate safety data are available to support a proposed product specification, conduct of a compound-specific risk assessment rather than a threshold-based evaluation is recommended. It is anticipated that, in most cases, higher product specifications would be supported from a safety standpoint when data are available to support a compound-specific risk assessment than would be through use of a threshold-based approach. In cases where the initial safety evaluation demonstrates a lack of genotoxic/carcinogenic or airway sensitization risk and the proposed specification is below the QT, additional risk assessment is not necessary.

In cases where the maximum expected human exposure to a leachable is expected to exceed DPAP’s qualification threshold of 5 µg/day, safety qualification for general toxicity concerns may be provided through evaluation of published toxicity data or relevant regulatory exposure limits such as US EPA air quality standards, or through the conduct of inhalation toxicology studies of an appropriate duration (e.g., at least 90 days duration for chronic indications). In some cases, data for chemicals with well-characterized toxicity profiles that
have a high degree of structural similarity to a leachable/extractable for which limited safety data
are available may be considered.

When toxicology data are used to support proposed product specifications, the most
relevant data should be considered. For example, if data are available from studies using both
oral and inhalation administration, the data derived from the inhalation studies are usually
considered to be most relevant. Safety margins for anticipated human exposures are calculated
based upon the NOAELs in animal studies. Generally, a 10-fold safety factor is applied for
cross-species extrapolation. In cases where safety data are only available from studies using the
oral route of administration, an additional 100-fold safety factor is applied, based on an
evaluation of a subset of the EPA HEAST database for which data were available following both
oral and inhalation administration. For this subset of chemicals, the presumed safe inhalation
doses derived from the RfCs were up to 100-fold lower than the identified reference doses
(RfDs) after conversion to a mg/kg/day dose. Therefore, a 1,000-fold safety factor (10 x 100) is
typically applied when using animal data from oral studies to support human inhalation use.

The PQRI Leachables and Extractables Working Group’s proposed process for safety
qualification of leachables incorporating use of the safety concern and qualification thresholds, is
shown in decision tree format in Figure 3. The decision tree supports FDA recommendations for
application of safety thresholds. Note that in some cases, decreasing the level of a leachable to
not more than the threshold can be simpler than providing safety data. Alternatively, adequate
data could be available in the scientific literature to qualify a leachable. If neither is possible,
additional safety testing should be considered. The studies considered appropriate to qualify a
leachable will depend on a number of factors, including the patient population, daily dose, and
duration of drug administration.
Figure 3. Decision Tree for Identification and Qualification. (a) If considered desirable, a minimum screen (e.g., genotoxic potential) should be conducted. A study to detect point mutations, in vitro, is considered an appropriate minimum screen. (b) If general toxicity studies are desirable, one or more studies should be designed to allow comparison of unqualified to qualified material. The study duration should be based on available relevant information and performed in the species most likely to maximize the potential to detect the toxicity of a leachable. On a case-by-case basis, single-dose studies can be appropriate, especially for single-dose drugs. In general, a minimum duration of 14 days and a maximum duration of 90 days
would be considered appropriate. (c) For example, do known safety data for this leachable or its structural class preclude human exposure at the concentration present?

The following case examples are presented to illustrate the safety qualification process.

Case 1. Bis-2-ethyl-hexyl sebacate (CAS RN 122-62-3)

The proposed product specification corresponded to a maximum daily human exposure of 9.1 µg/day (182 ng/kg/day for a 50 kg individual). The most relevant toxicity study identified for this compound was a published chronic dietary study in rats in which a NOEL of 200 mg/kg was observed. This dose corresponds to an acceptable human inhalation exposure of 0.2 mg/kg/day (200,000 ng/kg/day) after including a 1,000-fold safety factor for cross-species extrapolation and for the use of data derived from oral administration to support inhalation use. Even after incorporation of this safety factor, a greater than 1,000-fold safety margin for bis-2-ethyl-hexyl sebacate was present when comparing the acceptable human daily exposure to the maximum anticipated human exposure associated with the proposed product specification.

Case 2. 4-toluenesulfonamide (CAS RN 70-55-3)

The proposed product specification corresponded to a maximum daily human exposure of 60 µg/day (1200 ng/kg/day). In this case, the sponsor provided no supporting rationale for the proposed specification. However, a review of the literature indicated that only acute toxicity data were available. In this case, the DPAP requested that the sponsor lower the product specification to a level that corresponded to the Division’s safety qualification threshold of 5 µg/day or provide adequate toxicology data, such as a 90 day inhalation toxicity study, to support their proposed product specification.

Case 3. Acenaphthene (CAS RN 83-32-9)
The proposed product specification corresponded to a maximum daily human exposure of 0.067 µg/day (1.33 ng/kg/day). As in the previous case, only acute toxicity data were available. However, a State of Minnesota drinking water standard for acenaphthene is set at 400 µg/L (U.S. EPA Office of Water, Federal-State Toxicology and Risk Analysis Committee (FSTRAC) (November 1993). Summary of State and Federal Drinking Water Standards and Guidelines).

This standard corresponds to an acceptable daily inhalation exposure of 160 ng/kg assuming a daily intake of 2 liters/day, a 50 kg BW, and incorporation of a 100-fold safety factor for the use of oral data to support inhalation use. The calculated acceptable inhalation exposure for humans provided a greater than 100-fold safety margin, when compared to the maximum daily human exposure to acenaphthene through use of the drug product at the sponsor’s proposed specification. In addition, the anticipated human exposure was well below the DPAP’s safety qualification threshold of 5 µg/day.

Case 4. Nitrosamines

Nitrosamines can be present in certain rubber components of inhalation devices and are known carcinogens. In one product, six species were identified at various levels. The carcinogenic risk assessment was based on total nitrosamine exposure using the slope factor calculated for NMDA. A maximum human daily exposure of up to 0.04 ng/kg, a level associated with a cancer risk estimate of $10^{-5}$, was accepted based on the overall risk-benefit analysis and technological considerations, namely, the inability to manufacture rubber components that do not potentially leach nitrosamine compounds. Although the Division allowed a level that corresponded to a cancer risk estimate of $10^{-5}$, DPAP encourages sponsors to continue to reduce the potential for exposure and to strive to develop methods to eliminate the presence of nitrosamine compounds.
As stated previously, issues arising from the need for adequate safety qualification for leachables and extractables can often delay the approval of drug products. Therefore, some consideration should be given to addressing these issues earlier in product development or providing more substantive qualification information. Some ways in which the safety qualification process can be improved include the selection of materials to limit the number and level of potential leachables, the use of pre-extraction methods to lower potential exposures, and the submission of a clear rationale to support the safety of proposed product specifications. Often, the DPAP receives submissions containing only the proposed drug product specifications for a given leachable or extractable with no supporting rationale. It must be stressed that submission of an adequate supporting rationale often leads to a more efficient and expeditious review of a submission, with regard to the safety qualification of leachables and extractables.

V. Conclusion

The safety thresholds for leachables in OINDP developed by the PQRI Leachables and Extractables Working Group— a safety concern threshold of 0.15 μg/day and a qualification threshold of 5 μg/day— provide scientifically sound guideposts for industry and regulators to ensure, with a high degree of confidence, the safety of patients using these drug products. These thresholds were developed taking into consideration accepted safety thresholds for indirect food additives, impurities in drug substances, drug products, residual solvents, and genotoxic impurities in drug products. A scientifically sound process using well-established databases, risk assessment approaches, and literature information relevant to inhalation products was used to derive the thresholds. The Working Group also developed a recommended safety qualification process that incorporates application of the SCT and QT. This process supports FDA’s recommended processes for application of safety thresholds.
The PQRI thresholds and qualification process were developed with FDA regulatory support, and are expected to be used in pharmaceutical development programs and by regulators assessing drug applications. These scientifically justified thresholds will have a significant positive impact on the OINDP development and regulatory review process by removing uncertainty in the development process and directly linking safety with quality of OINDP.

VI. Acknowledgements

The authors thank the Product Quality Research Institute and the International Pharmaceutical Aerosol Consortium on Regulation and Science, and their member organizations, for support of this work.
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