

Application of the threshold of toxicological concern concept to pharmaceutical manufacturing operations

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Abstract

A scientific rationale is provided for estimating acceptable daily intake values (ADIs) for compounds with limited or no toxicity information to support pharmaceutical manufacturing operations. These ADIs are based on application of the “thresholds of toxicological concern” (TTC) principle, in which levels of human exposure are estimated that pose no appreciable risk to human health. The same concept has been used by the US Food and Drug Administration (FDA) to establish “thresholds of regulation” for indirect food additives and adopted by the Joint FAO/WHO Expert Committee on Food Additives for flavoring substances. In practice, these values are used as a statement of safety and indicate when no actions need to be taken in a given exposure situation. Pharmaceutical manufacturing relies on ADIs for cleaning validation of process equipment and atypical extraneous matter investigations. To provide practical guidance for handling situations where relatively unstudied compounds with limited or no toxicity data are encountered, recommendations are provided on ADI values that correspond to three categories of compounds: (1) compounds that are likely to be carcinogenic, (2) compounds that are likely to be potent or highly toxic, and (3) compounds that are *not* likely to be potent, highly toxic or carcinogenic. Corresponding ADIs for these categories of materials are 1, 10, and 100 µg/day, respectively.

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1. Introduction

A well-established methodology exists for setting acceptable daily intake values (ADIs) and safe levels of exposure in the workplace for active pharmaceutical ingredients (APIs) and associated intermediates when adequate toxicological data are available (Conine et al., 1992; Naumann and Sargent, 1997; Sargent and Kirk, 1988). These health-based limits are used to support both occupational health and quality programs in pharmaceutical research, development and manufacturing operations. The International Conference on Har-

monization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) is a joint regulatory and industry organization that has sought to improve the efficiency of drug development by focusing primarily on harmonization of safety, quality, and efficacy testing requirements for APIs among nations in the EU, Japan and the United States. Among the ICH guidelines are those that address the control of impurity and degradant levels in drugs (ICH, 1997a, 2002a,b,c, 2003), with acceptable amounts for residual solvents in pharmaceuticals, so-called “permitted daily exposure” (PDE) levels, calculated using a similar health-based approach (ICH, 1997a). Implicit in the ADI and PDE approaches is the concept that there exist daily dose levels that appear to be without appreciable

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risk of adverse effects in the population, including sensitive subgroups, for a lifetime of exposure (Dourson and Stara, 1983).

While other ICH safety guidelines address the standard battery of genotoxicity assays used for APIs (ICH, 1996, 1997b), no guidance is provided for determining acceptable levels for genotoxic impurities. The focus of this paper is to recommend ADIs, based on the “thresholds of toxicological concern” (TTC) concept, to support manufacturing quality operations, with specific application to cleaning validation and the resolution of atypical extraneous matter investigations for relatively unstudied compounds in APIs and finished pharmaceutical products when limited or no toxicity data are available.

When sufficient data are available for impurities or degradants, these data should obviously be used to establish a safe level of exposure. In such cases, formalized approaches for setting ADI values for noncarcinogenic chemicals have been in use for over 40 years (Lu, 1988), and it is a relatively straightforward process that includes procedures for identifying the critical adverse health effect and assigning the appropriate factors to a no-observed-adverse effect level (NOAEL) or lowest-adverse-effect level (LOAEL) to account for uncertainties (Dourson et al., 1996; IPCS, 2001), or alternatively, use of the benchmark dose method (Crump, 1984). This general approach has been well developed and accepted internationally by organizations that derive risk-based values. The limit-setting for carcinogens is a bit more problematic, and one that has evolved significantly over time (EPA, 1976, 1986, 2005; Mantel and Bryan, 1961).

However, until recently, toxicologists have faced limited alternatives when confronted with compounds with limited or no data. Some have found it necessary to extrapolate from data developed for similar compounds (by using toxicity data for surrogate compounds directly) or to make inferences using quantitative structure–activity relationship predictions. Alternatively, putative safe levels of exposure for subsets of chemicals or chemical groups as a whole have been used.

The TTC concept developed in recent years extends the ADI methodology to address substances that have very limited or no toxicity data, but for which reasonable exposure estimates can be made. The TTC principle (or the analogous FDA terminology “threshold of regulation”) was initially developed for food additives (FDA, 1995; Kroes et al., 2000, 2004; Kroes and Koziarnowski, 2002; Munro, 1990; Munro et al., 1996; Rulis, 1986), and has evolved and been adopted by the Joint FAO/WHO Expert Committee on Food Additives for flavorings (JECFA, 1993, 1995, 1999), although there is no conceptual reason why it cannot be extended to nonfood chemicals and chemicals that cause adverse effects via other exposure routes (e.g., parenteral routes).

In this paper, we provide a scientific and pragmatic approach to estimating ADIs for compounds in different

pre-established categories of a priori concern. Recommendations are provided below on acceptable daily intake values that correspond to three categories of compounds, for use when limited or no toxicity data are available: (1) compounds that are likely to be carcinogenic, (2) compounds that are likely to be potent or highly toxic, and (3) compounds that are *not* likely to be potent, highly toxic or carcinogenic. Corresponding ADIs for these categories of materials are 1, 10, and 100 µg/day, respectively. These categories address all types of toxicological endpoints, including carcinogenicity, immunotoxicity, neurotoxicity, and developmental toxicity. The thresholds for these categories are based on the assumption that, even if subsequent testing were to indicate that the compound were to fall into one of these three categories, exposures below the presumptive ADI level pose no appreciable risk to human health. An exception to these limits would be members of the “Cohort of Concern”—five structural groups of highly potent carcinogenic chemicals identified by Kroes et al. (2004) (i.e., steroids, polyhalogenated dibenzo-*p*-dioxins and -dibenzofurans, aflatoxin-like, azoxy-, and *N*-nitroso compounds).

2. Recommended thresholds of toxicological concern for relatively unstudied compounds in pharmaceuticals

2.1. Compounds that may be carcinogenic

An ADI value of 1 µg/day is recommended for compounds that are likely to be carcinogenic. The potential for carcinogenicity to humans is assessed based on *in vitro* mutagenicity data and/or a structural alert for genotoxic potential, and confirmed by an appropriate *in vivo* test (e.g., *in vivo* micronucleus test). However, structural alerts or evidence that suggests that a compound may be acting via a nonlinear or threshold mechanism would not be included in this category unless the threshold for such an effect was suspected to be low. Based on cancer potency estimates for hundreds of regulated carcinogens, the level of incremental cancer risk associated with lifetime exposure at this threshold value for a majority of compounds in this group is not likely to exceed one-in-a-million (1×10^{-6}), which is widely viewed as a *de minimis* level of risk. The 1 µg/day value is essentially identical to the 1.5 µg/day presented by Kroes et al. (2004) and proposed by the European Medicines Agency Committee for Medicinal Products for Human Use (CHMP, 2004) proposal for exposure to genotoxic impurities in chronically administered pharmaceuticals. In addition, as mentioned above, the 1 µg/day recommendation would not apply to compounds with structural similarity to compounds in a subset of highly potent carcinogens.

2.2. Compounds that may be potent or highly toxic

An ADI value of 10 µg/day is recommended for relatively unstudied compounds with limited data indicating they may produce pharmacologic or toxic effects at very low doses. For comparison, this recommended value corresponds to the lower end of the range of ADIs established for most pharmaceuticals. Compounds that show evidence of mutagenicity in *in vitro* studies, which is not confirmed by appropriate *in vivo* studies, are also included in this category. A positive *in vitro* study, in combination with a negative *in vivo* study, indicates the compound has genotoxic potential but the risk of cancer is considered to be at least 10-fold lower than the potential carcinogens in the first category at this level of exposure.

2.3. Compounds that are not likely to be potent, highly toxic or carcinogenic

An ADI value of 100 µg/day is recommended for relatively unstudied compounds that have no *a priori* evidence of unusual toxicity or potency and are not considered mutagenic (e.g., have no structural alerts and are negative in the Ames test). A chemical that has a structural alert, but is negative in an Ames test would be considered nonmutagenic, unless it is a member of a known structure/class that is not readily detected in the Ames test (e.g., benzene). In this special case, the compound would be bumped up into the category of potent or highly toxic compounds with an ADI of 10 µg/day. Otherwise, this recommendation is based on the range of health-based exposure limits (e.g., ADIs) established for chemicals on the basis of known systemic toxicity. The basic premise is that, even if a relatively unstudied compound were later shown to produce target organ effects, past experience indicates that the no-effect level for these effects would yield a health-based exposure limit greater than 100 µg/day using current risk assessment methods.

3. Basis for the proposed ADI values for categories of compounds with limited data

3.1. Regulatory precedents for carcinogens

The concept of establishing toxicologically negligible exposures, even in the absence of relevant toxicity data on a substance, has been around for more than three decades (Frawley, 1967). Nearly a decade ago, the FDA promulgated a rule defining a “threshold of regulation” for food contact articles of unknown toxicity (FDA, 1995; Munro, 1990; Rulis, 1986). In this rule, FDA established a value of 0.5 parts per billion (ppb) for food additives. Below this level, the agency considers

resulting dietary exposures to a food additive to be trivial, with negligible risk even if the compound were subsequently found to be carcinogenic. Proposed food contact articles meeting this threshold are exempt from the rigorous food additive listing regulation.

FDA based its “threshold of regulation” on an analysis of the Carcinogenic Potency Database (CPDB) established and maintained by Lois Swirsky Gold and others from the Lawrence Berkeley Laboratory (Gold et al., 1984, 1986a,b). At the time of its analysis, the CPDB used by the FDA contained more than 3500 long-term chronic animal studies of 975 chemicals (the current CPDB contains over 6000 experiments, Gold et al., 2005). The CPDB database is based on the TD50, a measure of carcinogenic potency that reflects the estimated dose required to induce tumors in 50% of experimental animals after correction for background tumors. FDA restricted its analysis to the 477 animal carcinogens that were the subject of oral feeding studies showing a statistically significant increase in the incidence of animals with specific neoplasms ($p < 0.01$) (FDA, 1993). If more than one TD50 value were available for a substance, the TD50 for the most sensitive site/species combination was chosen.

Based on its analysis, the FDA promulgated a threshold value of 0.5 ppb, which corresponds to an acceptable daily dietary exposure of 1.5 µg/day for an individual consuming 1500 g of solid food and 1500 g of liquids per day (Matthews and Machuga, 1995). Assuming that all, half, or 10% of chemicals are truly human carcinogens, such daily doses correspond to probabilities of 63, 82, and 96%, respectively, that the lifetime cancer risk would be less than a *de minimis* level of 10^{-6} if intake were at or below the respective intake levels (Munro, 1990). Reanalyses using more current CPDB datasets of more than 700 carcinogens did not significantly alter either the range of potencies or the peak position for the distribution (Cheeseman et al., 1999; Kroes et al., 2004). The TTC estimate is believed to be very conservative (health protective) because of the compounding effects of the numerous conservative assumptions used to derive the low-dose cancer risk estimates (Barlow et al., 2001; Kroes et al., 2004). Moreover, the TTC assumes a lifetime of exposure, whereas the application here is to manufacturing operations wherein there may be residual or *de novo* low-level impurities in a single or a few batches.

Recently, a TTC decision tree has been published for chemical substances in the diet that evaluates them in decreasing order of potency, and which establishes different TTC values for chemicals depending upon whether or not they are potentially carcinogenic (Kroes et al., 2004). Based on an analysis of 730 carcinogenic compounds, if a chemical has structural alerts for potential genotoxicity, but does not contain any of the five structural groups of concern, then the TTC would be

established at 0.15 $\mu\text{g}/\text{day}$. If the chemical lacked structural alerts for genotoxicity, a maximum TTC of 1.5 $\mu\text{g}/\text{day}$ would be established. Lower TTCs that are protective for other adverse health outcomes, and identical to values proposed earlier by Munro and coworkers (Munro et al., 1996), are incorporated into the decision tree.

As mentioned above, the European Medicines Agency Committee for Medicinal Products for Human Use recently solicited comments on a proposed TTC value of 1.5 $\mu\text{g}/\text{day}$ for genotoxic impurities in pharmaceuticals that have insufficient evidence for a threshold-related mechanism (i.e., that may be DNA reactive) (CHMP, 2004). Those chemicals with evidence of a threshold-related mechanism would be addressed through the standard no-observed effect level (NOEL) approach. Supporting the Kroes et al. (2004) analysis, the Committee acknowledged that this TTC corresponded to a risk of 10^{-5} excess lifetime risk of cancer, a somewhat higher risk than the traditional 10^{-6} de minimis risk level, but one that could be warranted by the corresponding benefits of pharmaceuticals.

Our proposed value of 1 $\mu\text{g}/\text{day}$ for potentially genotoxic carcinogens was derived independently of CHMP, yet very similar to their proposed value of 1.5 $\mu\text{g}/\text{day}$. In addition, our recommended values of 1, 10, and 100 $\mu\text{g}/\text{day}$ correspond to thresholds for the more potent of our internal occupational exposure level bands (Nauermann et al., 1996). Our application of the TTC concept to pharmaceutical manufacturing operations involving less than lifetime exposure scenarios (e.g., atypical investigations and cleaning validation) is intended to be a pragmatic yet health protective approach for even lifetime exposures. Our use of one significant digit reflects the precision of the underlying database and the inherent uncertainties in interspecies and low-dose extrapolation, and the rationale on which it was based.

In contrast to the TTC values and supporting analyses discussed above, Fiori and Meyerhoff recently conducted their own analysis of the distribution of TD50s from Gold's CPDB in an effort to develop de minimis levels for mutagens and carcinogens (Fiori and Meyerhoff, 2002). In their analysis, a target risk level (risk-specific dose (RSD)) was selected that corresponds to a de minimis excess lifetime cancer risk of one-in-a-million at the 95th percentile of the distribution of cancer potencies, assuming all compounds are carcinogenic. Not surprisingly, selection of such a very large percentile of the risk distribution and the presumption that all unstudied chemicals are carcinogenic compounds the other conservative assumptions and results in RSDs for mutagens (90 ng/day) and presumed carcinogens (9 ng/day) that are 17 and 170 times lower than FDA's threshold of regulation value of 1.5 $\mu\text{g}/\text{day}$, and 17 times lower than the TTC values from Kroes et al. (2004) for nongenotoxic compounds and potential genotoxic carcinogens other

than those in the Cohort of Concern. Fiori and Meyerhoff propose using their RSD to establish occupational exposure levels (OELs) at an excess lifetime cancer risk of one-in-one-thousand, and for cleaning limits for production equipment. For workers, they recommended levels of about 5 $\mu\text{g}/\text{m}^3$ (50 $\mu\text{g}/\text{day}$) for carcinogens and 50 $\mu\text{g}/\text{m}^3$ (500 $\mu\text{g}/\text{day}$) for mutagens, based on an assumption of less than lifetime exposure (e.g., 20 years). We believe the approach and threshold value adopted by the FDA and proposed by CHMP to guard against potential carcinogenicity are scientifically sound, adequately protective, and pragmatic for use with relatively unstudied compounds without imposing additional conservatism.

For the purposes of estimating thresholds of concern for compounds that are early in development and have not been fully evaluated as to their carcinogenic potential, the following inclusion criteria have been applied for the current analysis. Compounds are included in the "likely to be carcinogenic" category based on positive results in *in vitro* mutagenicity assays or a structural alert for genotoxic potential, and confirmed by an appropriate *in vivo* test (e.g., *in vivo* micronucleus test). However, structural alerts or *in vitro* testing information that suggests that a compound may act via a nonlinear or threshold mechanism would not be included in the presumptive carcinogen category, unless available data on potency support use of the lower category. For example, an experimental spindle tubule inhibitor would by default be included in the intermediate category of potent or highly toxic compounds with an estimated ADI of 10 $\mu\text{g}/\text{day}$, unless there were potency indications that suggested otherwise.

The decision to apply an ADI of 1 or 10 $\mu\text{g}/\text{day}$ takes into consideration available studies on the difference in potency between known genotoxic and nongenotoxic carcinogens. Based on an analysis of CPDB data, Cheeseman et al. (1999) noted that the most likely potency estimate for Ames negative compounds was approximately 8-fold lower than for Ames positive compound. Parodi and coworkers reported a clear difference in potency of approximately 50-fold when comparing median TD50 values for the most potent genotoxic and nongenotoxic compounds (Parodi et al., 1991). This result is in contrast to other published analyses that report minimal differences in median tumorigenic potency of genotoxic and nongenotoxic compounds (Brown and Ashby, 1990; Dybing et al., 1997; Tennant et al., 1987). Parodi et al. (1991) ascribe this difference to the spectrum of classes of compounds included in the different data sets that were evaluated, and the varying definitions of "genotoxic" and "nongenotoxic" that were used. Parodi et al. (1991) used a very stringent set of criteria to differentiate between genotoxic and nongenotoxic chemicals as compared to the analyses presented in the other papers. This result suggests that by using less strin-

gent criteria for defining “genotoxic” and “nongenotoxic” compounds to establish an ADI, many weakly genotoxic or nongenotoxic compounds may be misclassified and included in the carcinogen category, which is a health protective approach. It further suggests that placing marginally genotoxic or nongenotoxic compounds in a higher threshold category (i.e., 10 µg/day) is still health-protective, since there appears to be a difference in the potency of highly genotoxic carcinogens as compared to weak genotoxicants and nongenotoxic carcinogens. It is important to remember that if no observable toxic effects are evident in *in vivo* genotoxicity assays, typically performed at high dosages (e.g., 2000 mg/kg), then even if the compound were later discovered to be genotoxic, it would be unlikely to be very potent.

3.2. Regulatory precedents for noncarcinogens

In a rigorous effort to develop threshold doses of toxicological concern for noncarcinogens, Munro et al. (1996) evaluated NOELs for 611 substances from a diverse set of organic chemicals consisting of industrial, agricultural, environmental, and consumer chemicals, food substances, and pharmaceuticals and applied a simple 3-tiered structural classification scheme developed by Cramer et al. (1978). The structural classes they used were as follows:

- Structural Class I: Substances of simple chemical structure and efficient modes of metabolism that would suggest a low order of oral toxicity (e.g., L-glutamic acid, mannitol or propylene glycol).
- Structural Class II: Substances that are in a structural class in which there is less knowledge of the metabolism, pharmacology and toxicology, but for which there is no clear indication of toxicity (e.g., β-carotene, diallyl phthalate or maltol). Most substances belong to either of two categories; one includes substances with functional groups that are similar to, but somewhat more reactive than functional groups in Class I (e.g., allyl and alkyne); the other includes substances with more complex structures than substances in Class I, but that are common components of food.
- Structural Class III: Substances of a chemical structure that permit no strong initial presumption of safety, or that may even suggest significant toxicity (e.g., acetonitrile, 2,4-dinitrotoluene, chlorobenzene, or *p*-aminophenol).

The entries in Table 1 summarize the evaluations of toxicity data by Munro et al. for compounds in each of these classes, as well as compounds known to produce neurotoxic and developmental effects. Munro et al. (1996) chose a cutpoint representing the 5th percentile NOELs for the compounds present in each of the three structural classes. This approach was followed to ensure

very high (95%) confidence that “any other substance of unknown toxicity but of the same structural class as those comprising the reference database would not have a NOEL less than the 5th percentile for that particular structural class...” (Munro et al., 1996). From these NOELs, they calculated human exposure thresholds (equivalent to ADIs) of 1800, 540, and 90 µg/day (rounded to two significant digits), respectively, for the three classes by applying a composite uncertainty factor of 100 and assuming a 60 kg body weight. More recently, Munro et al. (1999) calculated a human exposure threshold of 2076 µg/day for developmental abnormalities based on the 5th percentile of the lowest toxic dose (TDLo) for 100 compounds in the Registry of Toxic Effects of Chemical Substances (RTECS) database. They also calculated a threshold value of 18 µg/day for 31 neurotoxic organophosphorus compounds (see Table 1).

For this analysis, a review was also performed of the ADI values derived for Merck active pharmaceutical ingredients (APIs) since 1981. These ADI values are used to support cleaning validation and to derive occupational exposure limits. The analysis excluded genotoxic compounds (e.g., certain process intermediates and cytotoxic antineoplastic agents) that would be included in the group of presumptive carcinogens. The remainder of the compounds ($N = 120$) are pharmacologically active materials with a broad range of potencies that are administered orally or parenterally. The compounds were distributed into three ranges of ADIs based on their pharmacologic potency: 79% ($N = 95$) had ADIs greater than 100 µg/day, 15% ($N = 18$) had ADIs between 10 and 100 µg/day, 5% ($N = 6$) had ADIs between 1 and 10 µg/day, and 0.8% ($N = 1$) less than 1 µg/day (see Table 1). In other words, 94% of the compounds with known pharmacologic activity had ADIs greater than 10 µg/day. Therefore, a relatively unstudied compound, in the absence of information suggesting that it would be an extremely potent drug, is unlikely to have an ADI of less than 10 µg/day once its pharmacologic potency is defined. Included for comparison in Table 1 are the FDA threshold of regulation value of 1.5 µg/day discussed above, and several percentiles of the ADI distribution for Merck APIs.

In addition, we performed an analysis of the distribution of oral reference doses (RfDs) from the US EPA Integrated Risk Information System (IRIS) database and Minimum Risk Levels (MRLs) from the Agency for Toxic Substances and Disease Registry (ATSDR). The US EPA establishes RfDs to guide the development of regulations for protection against noncarcinogenic effects of contaminants in environmental media (e.g., contaminated soil and drinking water). An RfD is defined as an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects

Table 1
Comparison of oral threshold values for adverse effects

Category	Number of chemicals in dataset evaluated	Human exposure threshold ($\mu\text{g}/\text{day}$)	Reference
Developmental abnormalities (5th percentile)	100	2076	Munro et al. (1999)
Structural Class I (5th percentile)	137	1796	Munro et al. (1996)
Structural Class II (5th percentile)	28	544	Munro et al. (1996)
Oral toxicity of RfDs and MRLs (25th percentile)	348	100	This analysis
Merck ADIs for APIs (21st percentile)	120	100	This analysis
Structural Class III (5th percentile)	446	88	Munro et al. (1996)
Neurotoxic compounds (5th percentile)	31	18	Munro et al. (1999)
Oral toxicity of RfDs and MRLs (10th percentile)	348	10	This analysis
Merck ADIs for APIs (6th percentile)	120	10	This analysis
FDA threshold of regulation value for carcinogenicity european medicines agency proposal	477	1.5	FDA (1995) and CHMP (2004)
Merck ADIs for APIs (1st percentile)	120	1	This analysis

during a lifetime (EPA, 2002, 2004). The lack of precision in this estimate reflects the incorporation of a series of uncertainty factors, including default values of 10-fold when data are not available to develop chemical-specific adjustment factors (CSAFs). The ATSDR has developed comparable risk values (referred to as MRLs) that are derived using similar principles (Pohl and Abadin, 1995; Pohl et al., 1998). MRLs are established for exposures of acute, intermediate and chronic duration. In Fig. 1 the cumulative distribution of RfDs and intermediate and chronic MRLs are shown in order to evaluate the extent to which the proposed category thresholds would be captured by the range of oral toxicities represented by the EPA and ATSDR risk values. When compared to the database of 348 risk values, a $10 \mu\text{g}/\text{day}$ threshold of concern is below 90% of the RfDs and oral MRLs, and the $100 \mu\text{g}/\text{day}$ threshold is below 75% of these values.

As mentioned earlier, the ICH has published a series of guidance documents on the evaluation of nongenotoxic impurities in drug substances (ICH, 2002a), drug products (ICH, 2003), and residual solvents (ICH, 1997a, 2002b,c). Each document has a specific focus, but each includes reporting, identification and qualification limit recommendations on allowable levels of impurities or concentration ranges below which no action is necessary. For example, for a maximum daily drug dose $\leq 2 \text{ g}/\text{day}$, the ICH reporting, identification and qualification limits for new drug substances are 0.05, 0.1 (or $1 \text{ mg}/\text{day}$, whichever is lower), and 0.15% (or $1 \text{ mg}/\text{day}$, whichever is lower) (ICH, 2002a). In other words, at this dose level, one could conceivably be exposed to $1000 \mu\text{g}/\text{day}$ of an unknown purity before testing to establish its identity and biological safety are required. For degradation products in new drug products, at a dose up to $2 \text{ g}/\text{day}$, the ICH reporting, identification

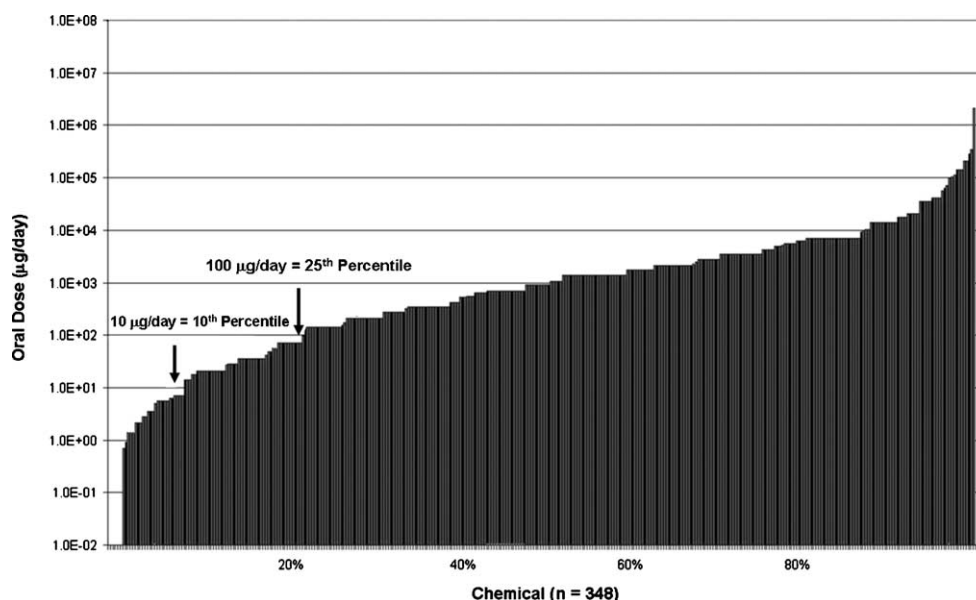


Fig. 1. Cumulative distribution of allowable non-cancer oral dose values.

and qualification limits are 0.05, 0.2 (or 2 mg/day, whichever is lower), and 0.2% (or 3 mg/day, whichever is lower) (ICH, 2003). Permitted daily exposure (PDE) values for Class II solvents (inherently toxic) listed in the ICH guidelines on residual solvents (Q3C Impurities) range from 0.5 to 48 mg/day (ICH, 1997a,b). The PDE for Class III solvents (low toxic potential) is 50 mg/day. The guidance document includes an appendix that provides additional background on the methods used to establish PDEs, which are consistent with current risk assessment methods for setting health-based limits (e.g., ADIs). Implicit in these limits is the presumption that these levels of impurities or degradation products are considered safe, levels far greater than the levels we propose as safe for relatively unstudied compounds found in APIs and residual contamination on process equipment.

FDA's recent guidance on this issue for generic drugs is also informative (FDA, 1999). According to this guidance document, if no potential for concern is indicated by QSAR evaluation, the impurity is considered qualified, but it should not exceed a level of 0.5% or 500 µg per day, whichever is less (equivalent to 500 µg in a 100 mg tablet), without other supporting data (such as genotoxicity test data). As in previous guidance on impurities, the scientific rationale for the recommended cutoff is not described.

4. Example application of the TTC concept to pharmaceutical quality operations

To demonstrate how the TTC concept might be applied to pharmaceutical quality operations, consider the example of a relatively unstudied compound for which there is a reasonable presumption that it may be potent or highly toxic. In this case, the recommendation is that potential exposures should be kept below 10 µg/day. If this contaminant could not be removed by reworking the batch and was present in the API at 10 ppm (10 µg in a 1 g maximum daily dose), that batch could be released. The contaminant could also be a residue in the process equipment, and a cleaning limit (calculated as an acceptable residue limit (ARL)) could be derived to assure that the material would not enter a batch of another API (API B) in unacceptable amounts using the following equation:

$$\text{ARL} = \frac{\text{ADI} \times \text{SBS} \times \text{SA} \times \text{RF} \times \text{CF}}{\text{MDD} \times \text{SSA}}$$

where ARL is the acceptable residue level (mg/swab), ADI the acceptable daily intake (µg/day), SBS the smallest batch size (kg), SA the swab area (cm²/swab), RF the recovery factor (unitless), CF the conversion factor = 1000 (unitless), MDD the maximum daily dose of drug (mg/day), and SSA the shared surface Area (cm²).

For a potent or highly toxic contaminant (ADI = 10 µg/day), a swab area of 25 cm², an RF of 0.5, a conversion factor of 1000, a 100 kg batch of API B with a maximum daily dose of 100 mg, and a shared surface area between API A and API B of 40,000 cm² yields:

$$\text{ARL} = [(1) \times (100) \times (25) \times (0.50) \times (1,000)] / [(100) \times (40,000)] = 3 \text{ mg/swab.}$$

By comparison, visual inspection and cleanliness requirements, which are used in combination with analytical test methods, typically result in visible residue detection limits well below 1 mg/swab (Forsyth et al., 2004). In each cleaning validation or atypical investigation, it would be incumbent on the plant to demonstrate, using worst-case assumptions, that the contaminant could not be present above an applicable threshold limit. Alternatively, the plant could develop and use a sufficiently sensitive analytical testing method to ensure that the contaminant level is kept below the applicable ARL.

5. Summary

Analyses of available data for regulated carcinogens and noncarcinogens were used to provide a scientific rationale for recommendations of ADI values for three classes of compounds with limited or no toxicity data. The robustness of the TTC principle is demonstrated by these oral ADIs, which consistently correspond well to low percentiles of the distributions of "safe" doses for compounds representing a diverse set of chemicals from different structural classes and encompassing a wide range of critical effects. The use of these values provides assurance that patients who may be exposed through product carry over to a second product made in shared equipment or through intake of products containing extraneous materials will be protected.

Our analyses of RfDs, oral MRLs, and Merck ADIs supplements the previous literature documenting the rationale for the thresholds of toxicological concern for different classes of chemicals for carcinogenic and noncarcinogenic effects. Collectively, these values support the reasonableness of the recommended threshold values of 1, 10, and 100 µg/day for pharmaceutical manufacturing for compounds with limited or no toxicity data. For perspective, an ADI of 100 µg/day is 6–484 times lower than the PDE values for Class II (inherently toxic) solvents, and 500 times lower than the PDE of 50 mg for Class III (low toxic potential) solvents listed in the FDA/ICH guidelines on residual solvents (ICH, 1997a). The recommended ADI of 100 µg/day for relatively unstudied compounds that are not likely to be potent, highly toxic or carcinogenic is also 10 times lower than the qualification threshold of 0.15% (or 1 mg/day, whichever is less) in the ICH guidelines for

impurities in new drug substances with a maximum daily dose of up to 2 g (ICH, 2002a).

For pharmaceutical quality operations, with few caveats, the recommended ADIs of 1, 10, and 100 µg/day provide an ample margin of safety for patients that may receive trace quantities of relatively unstudied compounds along with a drug product. Since these thresholds are based on the presumption of chronic exposure, their use in the context of an atypical event (which by definition is an isolated event) or in cleaning validation (subchronic exposure at worst) provides an additional margin of safety. Lower risk-based limits could be derived for acute or very short-term exposures.

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