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Potential impurities in drug substances: Compound-specific toxicology limits for 20 synthetic reagents and by-products, and a class-specific toxicology limit for alkyl bromides

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ABSTRACT

This paper provides compound-specific toxicology limits for 20 widely used synthetic reagents and common by-products that are potential impurities in drug substances. In addition, a 15 μg/day class-specific limit was developed for monofunctional alkyl bromides, aligning this with the class-specific limit previously defined for monofunctional alkyl chlorides. Both the compound- and class-specific toxicology limits assume a lifetime chronic exposure for the general population (including sensitive subpopulations) by all routes of exposure for pharmaceuticals. Inhalation-specific toxicology limits were also derived for acrolein, formaldehyde, and methyl bromide because of their localized toxicity via that route. Mode of action was an important consideration for a compound-specific toxicology limit. Acceptable intake (AI) calculations for certain mutagenic carcinogens assumed a linear dose-response for tumor induction, and permissible daily exposure (PDE) determination assumed a non-linear dose-response. Several compounds evaluated have been previously incorrectly assumed to be mutagenic, or to be mutagenic carcinogens, but the evidence reported here for such compounds indicates a lack of mutagenicity, and a non-mutagenic mode of action for tumor induction. For non-mutagens with insufficient data to develop a toxicology limit, the ICH Q3A qualification thresholds are recommended. The compound- and class-specific toxicology limits described here may be adjusted for an individual drug substance based on treatment duration, dosing schedule, severity of the disease and therapeutic indication.

1. Introduction

The synthesis of drug substances involves the use of reactive chemicals, reagents, solvents, catalysts and other processing aids, to form the structure of synthetic intermediates and ultimately the final drug substance. These compounds described in the synthesis pathways and reaction by-products may reside at low levels as impurities in the final drug substance. To prevent any safety implications from these potential impurities, acceptable toxicology limits are defined by toxicologists, and the chemical process is designed to control levels at or below the predefined limit.

Components of the syntheses may be mutagenic or carcinogenic.

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Given this potential toxicity an obvious question is, why not avoid their use? A recent survey of over 300 synthetic routes published in Organic Research and Development over a 10-year period (2001–2010) provides an overview of current synthetic strategies (Elder and Teasdale, 2015). It clearly demonstrates that syntheses of pharmaceuticals via complex, multi-stage pathways are not feasible without the use of reactive (including potentially mutagenic) reagents and intermediates, and thus, the focus should be on effective control as opposed to avoidance. The first requirement is to establish toxicology limits which then can be used as the basis for development of a control strategy.

Regulatory authorities acknowledge that the presence of impurities in the final active pharmaceutical ingredient (API) is unavoidable and consequently have published guidance documents related to their control. International Conference on Harmonisation (ICH) Q3A(R2) and ICH Q3B(R2) provide guidance for qualification and control for the majority of drug substance and drug product impurities/degradation products (ICH, 2006a, 2006b). ICH Q3C(R6) and ICH Q3D address requirements for residual solvents and elemental impurities (i.e., metals/catalysts), respectively (ICH, 2014, 2016). ICH M7(R1) is specifically focused on DNA-reactive (mutagenic) impurities, considering both safety and quality risk management in establishing levels that are expected to pose negligible carcinogenic risk to humans (ICH, 2017).

ICH M7(R1) covers the application of limits derived from acceptable intakes (AIs) based on the threshold of toxicological concern (TTC) for mutagens with insufficient carcinogenicity data to calculate compound-specific toxicology limits, and also addresses approaches to calculating compound-specific or class-specific toxicology limits when sufficient carcinogenic potency data exist (ICH, 2017). In the recent revision, ICH M7(R1), Appendix 3 was added to provide compound-specific toxicology limits for a series of mutagenic carcinogens, based on the assumption that the dose-response is linear; the document also illustrates derivation of limits for compounds whose mode of action (MOA) for the induction of tumors in rodents results in a non-linear dose-response, and is not considered relevant to human exposure at low doses. There is real value in establishing AIs for other common reagents/by-products beyond those listed in ICH M7(R1). Currently, industry sponsors develop their own toxicology limits and experienced toxicologists may reach different conclusions depending on the data considered and methodology used. Moreover, health authorities may generate a different toxicology limit, with potentially substantial implications for the synthesis and impurity control strategy that has been implemented based on a sponsor's internal toxicology limits. A few recent publications have proposed toxicology limits to encourage a consistent approach across the pharmaceutical industry, including for example: Antonucci et al., 2011; Eichenbaum et al., 2009; Ellis et al., 2013; Müller and Gocke, 2009; Parris et al., 2017; Snodin, 2010, 2015.

The basis for establishing appropriate toxicology limits relies on several common principles, including an understanding of the toxicological dose–response relationship and possible MOA. Regulatory evaluation of data on chemical toxicity can be considered under two broad categories:

(1) Sufficient experimental evidence for a MOA with a non-linear dose-response.
(2) Insufficient experimental evidence for a MOA with a non-linear dose-response and hence a linear dose-response is assumed.

The classification of linear or non-linear dose relation informs the type of toxicological data to be used to determine a toxicology limit is as follows:

(1) MOA with a linear dose-response: Is generally applied for these chemicals that are carcinogens with a likely mutagenic MOA through a DNA-reactive mechanism. An AI is derived following a linear extrapolation from the calculated cancer potency estimate in rodents, i.e., the TD_{50} (dose resulting in a 50% increase in tumors over background) or other accepted methods such as the Benchmark Dose (BMD) [BMD software available on https://www.epa.gov/bmds], resulting in an estimate with a predetermined increased incidence in cancer risk over background (Gaylor and Gold, 1995; Peto et al., 1984; USEPA, 2012) such as 1 in 10^5 for pharmaceutical impurities (ICH, 2017).
(2) MOA with a non-linear dose-response: Is generally applied for compounds that interact with non-DNA targets, and an appropriate toxicology limit is based on toxicity seen in repeat-dose studies, developmental and reproductive toxicities, and/or non-mutagenic carcinogenicity. The appropriate toxicology limit for chemicals with an established non-mutagenic non-linear MOA is called the permissible (or permitted) daily exposure (PDE) in ICH guidelines such as ICH Q3C(R6). It is calculated based on the identification of a no-observed-effect-level (NOEL) or no-observed-adverse effect-level (NOAEL) and use of adjustment ("uncertainty", "safety" or "modifying") factors (Sussman et al., 2016). However, there are instances where DNA-reactive chemicals can be demonstrated to exhibit a non-linear dose-response for mutagenicity with threshold or point of departure (PoD) below which no or negligible mutagenicity is expected (Gollapudi et al., 2013; Johnson et al., 2014; MacGregor et al., 2015a, 2015b).

ICH Q3C(R6), Q3D, and M7 provide toxicology limits for common residual solvents, elemental impurities (metals) and DNA-reactive mutagenic impurities, respectively. The solvents guideline derives one toxicology limit for all routes of exposure, while the metals guideline provides route-specific toxicology limits for the oral, parenteral, and inhalation route (in part because of low oral bioavailability for many metal compounds). For mutagenic impurities, ICH M7(R1) TTC-based toxicology limits are intended for all routes of administration, but ICH M7(R1) also illustrates individual cases where a route-specific AI is appropriate. The ICH M7(R1) guideline derives an AI for DNA-reactive impurities by linear extrapolation from the TD_{50} observed in carcinogenicity studies, and the PDE when the mutagenicity and/or carcinogenicity mode of action is considered as non-linear. This is in accord with the ICH Q3C(R6) solvent guidance, in which toxicology limits for certain carcinogenic class 1 solvents are calculated by linear extrapolation, while toxicology limits for the other solvents including non-genotoxic carcinogens use the non-linear, PDE approach.

The goal of this manuscript was to collaborate across pharmaceutical companies to develop compound-specific toxicology limits for commonly used chemicals reagents and frequently formed by-products in pharmaceutical syntheses. Also, we extended the analysis of alkyl chlorides made by Brigo and Müller (2011) that resulted in the adoption in ICH M7(R1) of a class-specific toxicology limit of ten times the default TTC-based AIs for monofunctional alkyl chlorides (ICH M7(R1), Note 5). Our assessment of alkyl bromide data demonstrated that a toxicology limit of ten times the default TTC-based AI is also appropriate for monofunctional alkyl bromides. We also provide examples of compounds sometimes assumed to be mutagens or mutagenic carcinogens (e.g., based on alerting structures for mutagenicity), where a careful analysis of the existing data does not support those assumptions, and examples of disproportionate concern over low level contaminants in solvents, in particular benzene. We include an example of developing toxicology limits for a carcinogen, which is endogenously produced in large amounts and also present in the diet (acetaldehyde).

Here we discuss the methodology used to generate toxicology limits, and the limitations and challenges experienced in developing such limits. Detailed monographs for each compound are provided in a Supplemental Materials. This article is intended to be a useful tool for the pharmaceutical industry and for regulatory scientists.

2. Methods

The general process for deriving compound-specific toxicology