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Limits of genotoxic impurities in medicines—a threshold and pragmatic approach

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The synthesis of pharmaceutical products frequently involves the use of reactive reagents as well as the formation of intermediates and by-products (Muller et al., 2006). Low levels of some of these impurities may be present in the final drug substance and drug product. These impurities may be chemically reactive and have the potential for unwanted toxicities including genotoxicity and carcinogenicity. In this presentation, a procedure for testing, classification, qualification, toxicological risk assessment, and control of impurities possessing genotoxic potential in pharmaceutical products is outlined. This proposal uses a staged threshold of toxicological concern (TTC) approach for the intake of genotoxic impurities over various periods of exposure. This staged TTC is based on knowledge about tumorigenic potency of a wide range of genotoxic carcinogens and can be used for genotoxic compounds, for which cancer data are limited or not available. The delineated acceptable daily intake values of between ∼1.5 μg/day for ∼lifetime intake and ∼120 μg/day for less than 1 month are proposed as virtually safe doses. These virtually safe doses imply exposures that do not pose an unacceptable risk to either human volunteers or patients at any stage of clinical development and marketing of a pharmaceutical product. The proposals in this presentation apply to all clinical routes of administration and to compounds at all stages of clinical development. It is important to note that certain types of products, such as those for life-threatening indications for which there are no safer alternatives, allow for special considerations using adaptations of the principles outlined in this presentation.

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Genotoxic contaminants in food—a risk assessment

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Substances that are genotoxic in vivo are not permitted for deliberate use in food production, whether as food additives, pesticides, veterinary medicines or in materials that come into contact with food. However, an appreciable number of known or suspected genotoxic carcinogens occur inadvertently in food, resulting from natural occurrence, environmental contamination, generation during cooking and processing, or occasionally as impurities in permitted food chemicals. Genotoxic substances are also produced from foods endogenously. Acrylamide, aflatoxins, arsenic, chloropropanols, ethylcarbamate, formaldehyde, heterocyclic amines, nitroso compounds and polycyclic aromatic hydrocarbons are just a few examples of carcinogenic contaminants that may be present in some foods. There has also been a number of well-publicised instances of azo dyes used as unauthorised colouring agents in spices. Whilst some of the substances are clearly genotoxic, determining a mechanism of carcinogenicity for others is not straightforward, and in the absence of evidence to the contrary it is often considered "prudent to assume" that genotoxicity is a contributing factor.

Long-standing advice from the UK Committee on Carcinogenicity of Chemicals in Foods, Consumers Products and the Environment (COC) is that a non-threshold approach should be adopted for risk assessment of substances that are genotoxic and carcinogenic, i.e. that there is some risk, albeit small, even at extremely low levels of exposure. The COC advises that mathematical models that attempt to provide a best estimate of cancer risk by extrapolation below experimental data points give an impression of precision which cannot be