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The toxicology of musk fragrances

Synthetic musk fragrances are widely used as replacements for natural musks not only in perfumes but also in soaps, toiletries and disinfectants. The worldwide annual production of musk fragrances ranges between 6000 and 8000 metric tons per year, of which nitro- and polycyclic musks represent 30 and 70%, respectively. As a result of their inherently low biodegradability, nitro- and polycyclic musks as well as their respective metabolites are persistent and have been detected predominantly in the aquatic environment. The presence of 'not-readily-biodegradable' compounds in the aquatic environment raised major concerns, primarily in Europe, where the horrendous impact of polychlorinated biphenyls (PCBs), especially on fish-otter (*Luttra luttra*) populations, is vivid in the memories of scientists, health officials and the public. However, moderate to high lipophilicity, slow biodegradation, and the presence in water, sediments and edible fish tissues does not automatically warrant the comparison of musk fragrances with PCBs. Indeed, only a thorough review of the available toxicological data in conjunction with analytical data from the environment allows appropriate judgement of the 'real' risks associated with these synthetic fragrance materials for humans and the ecosystem.

This view of the situation, and the need for a robust toxicological assessment of these compounds, led the European Union to include musk xylene and musk ketone on their third priority list under Council Regulation (EEC) No. 793/93, and the inclusion of these compounds in the OSPAR List of Chemicals for Priority Action. These official listings, and pressure from the public, also enticed toxicologists in industry, academia and in research foundations to invest time and capital to assemble already available toxicological data as well as to carry out new experiments. Most of the data that has come from the latter efforts is now assembled in this Special Topics Issue of 'Toxicology Letters'. Although this special issue does not claim to cover every conceivable aspect of toxicological assessment, it represents most of what we currently know about musk fragrance toxicity determined with state-of-the-art toxicological methodology and risk assessment processes.

As indicated above, a clear distinction has been made between the potential effects of musk fragrances in the environment (primarily the aquatic environment) and putative effects in mammals, i.e. humans. In order to maintain this distinction, this special issue was divided into two main sections 'I. Environmental Impacts and II. Mammalian Toxicology and Risk Assessment'. Both sections include reviews of the current literature, papers on new experimental data, and descriptions of risk assessment processes.

The first section dealing with the environmental impacts of musk fragrances is dominated by review articles regarding the presence of nitro- and polycyclic musk fragrances in the environment (Rimkus, 1999; Rimkus et al., 1999) and elaborate

risk assessments on the impact of polycyclic musk fragrances (Balk and Ford, 1999a,b). Only two basic research articles are present in this section (Chou and Dietrich, 1999a,b). This should not, however, give the impression that all necessary work for a robust toxicological assessment of the impact of musk fragrances in the environment has already been done. In reality, the data base presently available is still rather meager, primarily made up of routine acute and subchronic tests involving species delineated as necessary (algae, zebrafish, fathead minnow and rainbow trout) in the OECD guidelines or EU-TGD (Tas et al., 1997). Data on chronic exposure, or on endpoints other than lethality, growth, tissue damage and toxicokinetics are lacking. Despite this caveat, the data presented in the 'Environmental Impact' section show quite clearly that adverse effects of musk fragrances in the environment are not imminent at the environmental concentrations currently detected. Yet the data also demonstrate that decisive species differences in susceptibility exist which certainly merit further investigation, especially with chronic exposure scenarios. Furthermore, the fact that metabolites of nitro musks appear in higher concentrations in the environment than do their parent compounds (Rimkus et al., 1999) and also seem to have greater biological activity (Chou and Dietrich, 1999a), certainly emphasizes that routine toxicological assessment of environmentally persistent compounds is not sufficient for a thorough environmental risk assessment. Overall, the data presently at hand indicate that there appears to be no imminent danger from environmental contamination with musk fragrances. Despite this, effects such as endocrine modulation, chronic organ toxicity, behavioral alterations, immune suppression, etc., which have the potential to affect the population to a much greater extent, should be investigated and hopefully ruled out as being of any toxicological significance in the near future.

In contrast to the situation with environmental data, an impressive database for mammalian toxicology has become available over the past few years. The peer-reviewed data assembled in this special issue reflects work done in both academic and industrial settings. The divergent views reflected by these different researchers are important in coming to a consensus on the impact of the data presented for animal and specifically human health risk assessment. It is very comforting to realize when reading the papers in this section that, despite minor disagreements, the general tenor is the same: musk fragrances, whether nitro-substituted or polycyclic, do not presently appear to pose a risk for human health. Indeed, only single applications of very high doses, never occurring in the final products, of the polycyclic musk AHTN shows demonstrable toxicity (Steinberg et al., 1999). In addition to oral exposure (Api and Ford, 1999; Steinberg et al., 1999; Suter-Eichenberger et al., 1999), the effects of subchronic dermal (Ford et al., 1999; Hawkins and Ford, 1999) and inhalation (Fukayama et al., 1999) exposure to parent compounds and fragrance mixtures were investigated. Neither of the studies reported toxicological data that would immediately raise concerns. Indeed, none of the compounds tested in rodents demonstrated prolonged systemic residual times or bioaccumulation and therefore did not appear to be of critical concern. The latter view is not contradicted despite the earlier findings of Riedel and coworkers (Riedel and Dekant, 1999; Riedel et al., 1999), and Helbling and coworkers (Helbling et al., 1994; Kokot-Helbling et al., 1995) demonstrating that musk xylene can form hemoglobin adducts in humans and, contrary to findings in rats, has a long half-life (estimated at ~ 80 days). Indeed, neither nitro- nor polycyclic musk fragrances have any genotoxic activity when tested with the routine systems available (Api et al., 1995, 1996; Emig et al., 1996; Steinberg et al., 1999).

Musk xylene and musk ketone are inducers of the cytochrome P450 enzymes in mice and the pattern of induction is consistent with that observed with phenobarbital, the classical CYP2B inducer and mouse liver carcinogen (Lehman-McKeeman et al., 1995, 1997). However, additional work by Lehman-McKeeman et al. (1999), as presented in this special issue, demonstrates that the pattern of cytochrome P450 induction in rats is dissimilar to that in mice, thus corroborating the presently uncontested view that musk xylene-induced liver tumors in mice are mouse-specific

and have little or no relevance for humans. Similarly, the data on the developmental toxicity of nitro- and polycyclic musks (Christian et al., 1999; Suter-Eichenberger et al., 1999) and the potential endocrine modulating-activity of the polycyclic musks AHTN and HHCB (Seinen et al., 1999) do not portray a disquieting picture. Nevertheless, in view of the fact that nitro musks appear to have a much longer half-life in humans than in rodents, show hemoglobin adducting activity, and that AHTN and HHCB both show weak estrogenic activity in transiently estrogen receptor α (ERα) or β (ERβ)-transfected human embryonal kidney cells (Seinen et al., 1999), further toxicological investigations, especially with regard to the chronic effects of nitro- and polycyclic musks in humans, appear warranted.

We hope that this special issue of 'Toxicology Letters' will give readers a more detailed understanding of the, in some cases, quite complex toxicology involved with musk fragrances. We would like to thank all contributing authors for their efforts and especially the referees for their input and constructive comments.

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