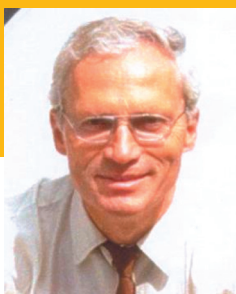


MNF Interview

with Gerhard Eisenbrand,
University of Kaiserslautern



The health risk of nitrosamines

Toxicologist Prof. Gerhard Eisenbrand, University of Kaiserslautern, Germany, is the Chairman of the Senate Commission on Food Safety (SKLM) of the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation). His research interests are environmental and food toxicology, mechanisms of action of genotoxic agents, metabolism, experimental chemotherapy and anticancer drug development. Prof. Eisenbrand is a well-known expert in the field of nitrosamines.

MNF:

Prof. Eisenbrand, in this issue of MNF (page x-xx) there is an article about the occurrence of nitrosamines in rubber products, such as balloons and condoms. How toxic are nitrosamines to human health?

Eisenbrand:

Although nitrosamines are amongst the strongest carcinogens known, their acute toxicity is only moderate or even low. There are just a few anecdotal reports an acute poisoning of humans, either accidentally by inadvertent working place exposure or within a criminal poisoning context. In contrast, their high carcinogenic potency has been proven in animal experiments on many different species, from aquarium fish to subhuman primates. Virtually no species has been found to be resistant to the cancer-inducing potential of these compounds. Moreover, it also has been shown that the metabolic activation of nitrosamines into DNA-damaging electrophilic agents is very similar in animal and human tissues, and that this metabolic activation results in the induction of similar mutagenic DNA lesions. In other words, although direct proof of carcinogenicity to humans is not available, the evidence is overwhelming that these agents should be considered as human carcinogens, in line with the assessments of the International Agency for Research on Cancer, IACR, Lyon in France.

MNF:

Do you expect that nitrosamines released from balloons or condoms are absorbed by humans via mucous membranes?

Eisenbrand:

Nitrosamines can easily penetrate the skin of experimental animals and humans, as has been proven convincingly in a series

of skin penetration studies. Since the permeability of mucous membranes is considerably higher than that of skin, there is no reason to believe that nitrosamines released from balloons or condoms are not rapidly absorbed through the mucous membranes they come into contact with.

MNF:

The authors found that over 80% of the sampled balloons contain more than the recommended nitrosamine level of 10 µg/kg material. Furthermore they estimated that in the worst case, if highly contaminated condoms are used, the exposure from condoms might exceed the nitrosamine-exposure from food. Is there a human health risk from balloons and condoms?

Eisenbrand:

Since nitrosamines are very strong carcinogens, any exposure should be considered to be connected with some degree of human health risk. However, for risk minimization, an upper level of nitrosamine release from such rubber products of 10 µg/kg material under simulated use conditions has been set in the European community. This is in accordance with the “ALARA” principle for minimizing exposure, which means “as low as reasonably achievable”. It reflects the state of the art in terms of good manufacturing practice and ensures that exposure, even under worst-case situations, would be substantially less than background exposure from the diet and thus does not significantly augment total exposure.

MNF:

Nitrosamines were not detectable in a few samples. What can the manufacturer do to minimize the concentration of nitrosamines and nitrosatable compounds in rubber products?

Eisenbrand:

The fact that in some samples nitrosamines were not detectable clearly shows that such products can be produced without nitrosamine contamination. It has been well-known for a long time that some chemicals used in the vulcanization process, e.g., certain vulcanization accelerators, stabilizers, retarders and other additives, generate nitrosamines under certain production conditions. Alternative chemicals not giving rise to carcinogenic nitrosamines are available and should be used exclusively.

MNF:

Nitrosamines require metabolic activation by cytochrome P450 enzymes to form the ultimate carcinogens. Is this process influenced by other food constituents or pharmaceuticals?

Eisenbrand:

The cytochrome P450 enzyme family is the most important tool given to us by evolution to clear the body of lipophilic compounds. Without this CYP450-mediated functionalization in connection with further enzymatic coupling reactions, our organism would lack a defense system of pivotal importance. Thanks to nature the CYP450 system handles an extremely broad substrate spectrum. It is therefore understandable that it can be influenced by many natural or synthetic compounds, be it food constituents, drugs or others. This influence can be in

“Nitrosamines can easily penetrate the skin of experimental animals and humans, . . .”

both directions, inhibitory or stimulatory and very often both effects occur at the same time. In short, such modifying effects are quite adequately described experimentally but often are difficult to predict in the normal human exposure situation.

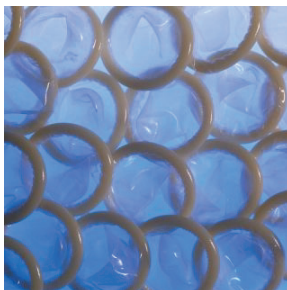
MNF:

Nitrosamines can easily be formed by the reaction of amines and nitrosating agents, *e.g.*, sodium nitrite, found in many foods. How much is known about the endogenous formation of nitrosamines in the gastro-intestinal tract of humans?

Eisenbrand:

It has been well established by experiments in animals and humans that nitrosamines can be formed from precursor compounds in the gastro-intestinal tract by a process called endogenous nitrosation. By feeding animals easily nitrosatable precursor amines such as morpholine together with nitrite, the same tumors are generated as after exposure to N-nitroso morpholine. In humans endogenous nitrosation can be followed by applying appropriate amino

acids, such as proline, that give rise to noncarcinogenic nitroso compounds. In the case of proline, the endogenously formed N-nitrosoproline can be measured in the urine since it is excreted quantitatively.



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MNF:

In some countries there are recommendations for maximum nitrosamine concentrations. Do you expect maximum limits for nitrosamines in balloons and condoms in the EU?

Eisenbrand:

Indeed, I do expect the setting of maximum limits for nitrosamines and nitrosatable compounds in such products in the EU in due course.

MNF:

Prof. Eisenbrand, thank you very much for this interview.

Interview by Hans-Ulrich Humpf