7.7. Safety Factors

If toxicity or an epigenetic carcinogenic effect of possible relevance to man is found, the single most important parameter to evaluate is the no-observed-adverse-effect-level (NOAEL) for toxic or carcinogenic effects in relation to the exposure. Is there a sufficient safety factor defined as exposure at the NOAEL in the most sensitive species (as far as this species is of relevance to man) relative to the maximal human exposure (dose/concentration and duration of exposure) occurring or intended? For the reasons given below, no strict rules are available. Generally, a safety factor of 10 for extrapolation from animal to man and an additional safety factor of 10 for inter-individual variation in man (for a total safety factor of 100) is considered acceptable. However, there are many compounds on the market with a considerably lower safety factor.

The *therapeutic indication* of drugs is particularly important. Lower safety factors are acceptable for life-saving indications compared to non life-saving indications. In general, higher safety factors are needed when children or young adults are the target treatment population, compared to medications used for patients towards the end of their natural life span. Are potentially safer alternatives available or has the substance in question a true advantage over the alternatives that would justify a minimal risk? How did regulatory authorities assess similar findings with other drugs? For chemicals other than drugs, generally none or limited human data are available. Furthermore, exposure to these agents happens accidently or through contamination. Therefore, risk assessment tends to be more conservative for agrochemicals (304), other environmental chemicals (220,284), consumer products (305), residues in food (306), and chemicals at the workplace (307). The general principles are also summarized in textbooks of general toxicology or in various publications (e.g., Ref. 308).

Especially high safety margins are required for compounds that induce lesions which are considered irreversible. Lesions in the category include necrosis of neurons and ocular changes (particular retinal degeneration or degeneration of the lenses).

Certain authorities are also very cautious in case of toxicity to the reproductive organs, which could lead to sterility (besides the possibility of teratogenic effects).

8. REPORTING

8.1. Study Report

Good reporting of potentially adverse effects, including a candid discussion and scientifically sound conclusions are very important.

The *method section* must include a good description of the procedures followed during the study and for the evaluation. In particular, the