

## ANNEX 5

### COC GUIDANCE ON RISK ASSESSMENT FOR CARCINOGENICITY

Risk assessment of chemical carcinogens is dependant on the mechanisms of carcinogenicity and the relationship between dose and tumour response. For most non-genotoxic carcinogens it is accepted that there is a threshold dose, below which no effect is observed. Many non-genotoxic carcinogens induce tumours as a secondary adverse effect arising from an initial toxicological effect, which has a threshold. It follows that for these substances there is no carcinogenic risk at dose levels that do not produce the primary toxicological event, ie at doses below the threshold.

Therefore, where there is adequate evidence to support a threshold for carcinogenicity (ie the compound and metabolites do not have in-vivo mutagenic activity and there is an adequate evaluation of the mode of action for tumours observed in animal studies), the Committee believe that an approach based on the use of uncertainty factors should be adopted.

For genotoxic carcinogens, a non-threshold approach is advocated. The Committee concludes that it is inappropriate to model dose-response data for the estimation of risks at human exposure doses due to considerable uncertainties underlying the approaches used and with regard to the carcinogenic process.

In relation to asbestos-induced cancer, the mechanism by which tumours arise (in the lung and the mesothelium) remains uncertain but is most likely to involve inflammatory processes. Whether or not a threshold or non-threshold approach is advocated, the COC position is that it is inappropriate to estimate human cancer risk via modelling dose-response data.