interstrand crosslinks were detected at 2 μM fec-12. Higher doses of fec-12 also caused DNA single strand breaks, DNA protein crosslinks and alkali-labile sites. Dose-effect studies indicate both the high reactivity of fec-12 towards cellular thiols and DNA, and that cellular thiols are of crucial importance in protecting human cells against fec-12-induced DNA damage.

CHANGES IN GLYCOSAMINOGLYCAN SYNTHESIS AND CELLULAR ADHESION ASSOCIATED WITH INCREASSED METASTATIC POTENTIAL OF MELANOMA CELLS

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In order to determine if compositional or structural changes of glycosaminoglycans (GAGS) are associated with the metastic efficiency of tumour cells, we have examined the composition of GAGS, and the properties of heparans synthesised by B16F1, F10 and BL6 melanoma cells, in addition to cellular adhesion studies.

The poorly metatatic cell line B16F1 synthesised a higher proportion of non-sulphated GAGS compared to those synthesised by the metastatic F10 and BL6 cell lines. However, there was no significant difference in the composition of the sulphated GAGS between the three cell lines. Heparans from the metastatic F10 and BL6 cells bound more tightly to DEAE-cellulose columns than the heparans isolated from the F1 cells. The metastatic cells synthesised heparans of a higher molecular weight, while there was no detectable difference in the degree of sulphation. The B16F1 cells exhibited only poor cell-cell adhesion when seeded on agar compared to the F10 and B16 cells, while all three cell lines eventually formed spheroid-like structures when seeded on basement membrane gel. The observed changes in the GAGS may contribute to the arrest or attachment of tumour cells to the endothelium of the target organ.

CARCINOGENICITY AND MUTAGENICITY STUDIES IN NEW DRUG APPLICATIONS

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The Nordic guidelines on new drug applications specify a detailed list of mutagenicity and carcinogenicity data required for the registration of drugs intended for chronic use, e.g. non-steroidal anti-inflammatory drugs (NSAIDs). I have analysed the data available to the Finnish licencing authority on NSAID applications submitted during 1976-83. The criteria used were quantitative, so the technical and scientific aspects of the test procedures did not fall within the scope of the study.

Mutagenicity studies were included in 33% of applications according to the guidelines, 33% were inadequate and 33% of applications did not contain any data on genotoxicology at all. Carcinogenicity studies were reported adequately in 39% of applications, but 39% were inadequate and 22% of applications failed to document any carcinogenicity studies.

The analysis of mutagenicity and carcinogenicity data revealed clear defects. Inadequacies in documentation lead to enquiry of additional data which prolongs registration times. However, the proportion of adequate applications increased as a function of time during 1976-83.

CELL PHENOTYPE INSTABILITY IN PRENEOPLASTIC FOCI OF RAT LIVER

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Carcinogenesis is a multi-step process in which genetic-phenotypic instability and sequential selection of preneoplastic cells for increased growth capacity and other neoplastic characteristics are essential phenomena. During chemical carcinogenesis in rat liver, the development of enzyme defficient foci, their clonal origin and their relationship to tumour formation are known. We report the results of four carcinogenesis protocols consisting in one or two cycles of diethylnitrosamine and phenobarbital. Histochemistry for three enzymes on serial sections has revealed seven different kinds of homogeneous liver foci resulting from simple and combined enzyme deficiencies and also heterogeneous foci showing small foci inside. We consider such secondary foci as subclones originated from cells already modified that have developed an additional phenotypic change. Some of such foci develop after the first cycle if the promotion phase is as long as 57 weeks but their appearance is much more important after a second cycle. Comparing the number of foci per surface area of liver section with the number of secondary foci per surface area of focus section, it seems clear that cells already modified are less stable than other hepatocytes, showing a