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EFFECTS OF CYCLOPHOSPHAMIDE AND ITS METABOLITES ON THE DIFFERENTIATION OF MOUSE EMBRYOS DURING THE PREIMPLANTATION PERIOD *IN VIVO* AND *IN VITRO*

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To evaluate the effects of drug treatment during the first days of pregnancy pregnant mice received a single injection of cyclophosphamide (CPA) 36 hr before implantation. The teratogenic effects were studied at term, during organogenesis and before and during implantation. After application of 20-80 mg/kg CPA a dose-dependent increase in the resorption rate was found at term, but no malformed fetuses. The somite number and wet weight of treated embryos were determined during organogenesis. These growth parameters indicated a developmental retardation of about 24 hr. Determination of the time of implantation showed that this retardation was not due to delayed implantation. Embryo transplantation experiments and *in vitro* culture of blastocysts beyond the time of implantation showed that the early CPA treatment interfered dose-relatedly with subsequent development of both, the embryo and the decidual reaction of the uterus. *In vitro* culture of 4- and 8-cell mouse embryos to the blastocyst stage in the presence of CPA and its metabolites acrolein, phosphoramide mustard and 4-hydroxy-peroxy-CPA indicated that phosphoramide mustard probably is the most important embryotoxic metabolite of CPA during early pregnancy. The cell number of blastocysts in CPA treated animals was decreased dose-dependently already 24 hr after treatment. When in additional studies the size of the inner cell mass (ICM) was determined from which the embryo proper is developing after implantation, again a dose-related decrease in the cell number of the ICM of blastocysts was found. Our studies on the effects of CPA treatment during the preimplantation period demonstrate the following developmental abnormalities in blastocysts of treated animals already before implantation: cell number, size of the ICM and developmental potency are reduced dose-dependently in such blastocysts.

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QUALITATIVE AND QUANTITATIVE ANALYSIS OF PCB-RESIDUES IN CATS

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After oral and i.v. (portal vein) application of a purified technical PCB-mixture (Chlophen A 30, degree of chlorination 42 % w/w), the residues in liver, muscle and fat tissue of cats were analysed. Capillary gas chromatography and electron capture detection were used; the main components of the mixture were identified by combined GC-MS.
After infusion (30 min), the maximum concentration in the fat tissue was reached only after 4-48 hours, after oral application, however, after 1-5 days. In the muscle, the maximum concentration was observed 1-2 days earlier. The elimination half-time (observation period 56 days) was for Cl_4- and Cl_5-biphenyls less than 1 day, for Cl_3-biphenyls less than 5 days and for Cl_4-biphenyls less than 10 days (exception: Cl_4-component, R_t=2005,8 $T_{1/2}$=18 d). The identified Cl_5-biphenyls showed $T_{1/2}$ of up to 25 days, Cl_6-biphenyls $T_{1/2}$ of 20-40 days, only 2,3,6,2',3',6'-Cl_6 was eliminated much faster ($T_{1/2}$=4.3 d). For higher chlorinated components $T_{1/2}$ values of more than 60 days must be estimated.

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MASS FRAGMENTOGRAPHIC STUDY OF THE PHARMACOKINETICS AND TISSUE DISTRIBUTION OF DIMETHYLETHER (DME)

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As DME is accepted as an important alternative for fluorocarbon propellants in aerosols, investigations on the pharmacokinetic behaviour and tissue distribution are necessary in order to obtain information on potential toxicological risks.
During and after intratracheal application of air containing up to 2000 ppm DME to rats, DME tissue concentrations in blood, heart, lung, liver, spleen, kidney, fat, muscle and brain were measured up to 180 min. The DME concentrations were determined by means of head space gaschromatographic - mass fragmentographic methods in single-ion-detection mode (SID) at m/e 46, using diethylether as an internal standard. The increase of the DME concentrations during the exposure is very rapid and nearly uniform in all organs. There is only a little retardation concerning fat and muscle tissues according to a slower dissipation process. Within 30 min. a steady-state-level (16.4 ± 1.4 ppm (n=16) at 1000 ppm DME in the respiratory air) is reached in all organs except muscle tissue, where the DME concentrations do not exceed 8 ppm. In contrast to the behaviour of diethylether, there is no remarkable accumulation in adipose tissues because of the relatively low lipophilic properties of DME.
The elimination is to be described by model calculations as a biphasic process, which is characterized by $t1/2\alpha$ = 10 min. and $t1/2\beta$ = 90 min. respectively.
Investigations on DME blood levels in man after DME-aerosol-spray applications show very low levels of 20-50 ppb after a short-time exposure, whereas an inhalation of air containing 300 ppm DME for 15 min. results in blood levels of about 0.5 ppm.

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EFFICACY OF PARAFFIN, CHARCOAL, CHOLESTYRAMINE AND AMBERLITE ON HYDROCARBON INGESTION: COMPARATIVE KINETIC STUDIES WITH ^{14}C-BENZENE IN MICE

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Considering the wide clinical use of paraffin in the therapy of hydrocarbon ingestion, the experimental data on the efficacy of this procedure seems to be rather poor. Furthermore contradictary results are present in the literature. Under rigorous standard conditions we investigated the absorption, plasma and tissue concentration of ^{14}C-benzene by use of radiospectrophotometrical methods. Mice fasted 6 hrs were anaesthitized with urethane and given 500 µl benzene per kg body weight (b.w.) intraduodenal. Paraffin and the other substances listed above were administered simultaneously as well as 15 min after the application of benzene. The time of investigation was 1 1/2, 5, 15, 45 and 90 min. Corresponding to these time periods 61.3, 91.5, 117.0, 329.0 and 473.5 µl /kg benzene was found to be absorbed in controls. Under paraffin (10 ml) charcoal (0.5 g), cholestyramine (1.0 g), and amberlite (1.0 g) per kg b.w. these values were significantly reduced. At the same time the concentration of ^{14}C-benzene in plasma and tissue were found to be smaller than in controls. The latter effect was most pronounced after short time intervals. The protective activity of all substances was somewhat smaller when they were administered 15 min after benzene application. Above all, charcoal proved to be the most potent inhibitor of benzene absorption.

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