Mathematical algorythms for complex risk assessment
of 2,3,7,8-tetrachlorodibenzo-para-dioxin.

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Exist uncertainties in dioxin risk assessment don't assist the process of operative decision-making in the risk management. One of the ways to get over these difficulties is the development of complex mathematical models or decision support systems that are able to use all information about dioxin' properties for the analysis and synthesis od objective conclusions.

It is known that optimal scheme of dioxin risk assessment is to consider toxicokinetics of the dose, to estimate biologically effective dose and to assess the "dose-response" relations[1]. But it is very difficult problem to realize this scheme for the human health damage forecasting.

We suggest the first version of the system of two mathematical models for the complex assessment of toxicokinetics and toxicodynamics of dioxin in the human body and forecasting some effects of its exposure.

Model QUANT (QUANtity of Toxicant) represents the multicompartmental physiological pharmacokinetic model describing absorption, distribution, fate, metabolism, and elimination of dioxin in the human body. The model allows to estimate concentrations of TCDD and its metabolites in 17 organs, tissues, excretes (urine, feces, bile, milk), and to assess the quantity of ligands "dioxin - Ah-receptor" in target organs/tissues (liver, thymus, blood cells, red bone marrow). Input information for the model is the character of dioxin exposure: single dose, multiple constant dose, multiple changed dose, inhaled, ingested, percutaneous application (simultaneous or in different combinations).

It may analyse toxicokinetics and toxicodynamics of dioxin in different groups of the human population: 3 groups of children (between birth and 12 years old), teenagers, men and women more than 18 years old and also pregnant and nursing women. Separate subroutine analyses toxicokinetics in the embryo/fetus body on all studies of its prenatal development.

Specific parameters are "blood-tissue" partition coefficients and quantity characteristics of interaction of the chemical or its metabolites with receptors in target tissues.

Mathematical model CLEVER (Complex LEVEl of Risk) predicts effects of exposure of TCDD on human health. The model is based on the data of epidemiological and experimental researches

selected by experts for finding out dependence between the dose and all possible effects.

Using data about the value, duration of exposure and application of the dose of dioxin as input information CLEVER allows to forecast: risk of carcinogenic, embryotoxic, fetotoxic, teratogenic, and other effects.

In the case of single exposure QUANT forecasts the excretion half-life to be between about 6.5 year (for babies) and 9.5 year (for adults). The excretion half-life for humans has been reported to be 5-9 years[2]. In the case of multiple exposure of comparatively small doses (0.1-10 pg/kg/day) concentrations in the adipose tissue are similar to background levels of dioxin content for human populations in the industrial countries[3]. The more a summary dose (when prolonged chronic exposure takes place) the more differencies between the dose and the concentrations of ligands "dioxin - Ah-receptor" in the target tissues and organs. It shows the necessity to find approaches to use biologically effective doses in the "dose-response" relationships.

Input and output information of model CLEVER is presented in the table.

The incidence of porphyria cutanea tarda is based on the data about changes of daily content of porphyrines and aminolevulinic acid in urine and changes of hematological and blood biochemical parameters both for humans and animals. The incidence of chloracne may be connected with the dynamics of SGPT activity and concentrations of cholesterol and triglycerides[4-6]. All these relations had been interpreted by experts and integrated into the system. Therefore CLEVER is developed as expert system that is based on very detailed information, and demonstrates a goog agree with the data reported.

The important advantage of the system is that it allows to estimate effective concentrations of TCDD. But now it is clear unsufficiently how to connect a biologically effective dose and a response because there are no full data about the relation between concentrations of ligands "dioxin - Ah-receptor" in the target tissue and concrete parameters of the effect.

In our opinion, now it is important to create model systems allowed to study the complex of processes and factors that defind toxicants' levels in the environment, doses and effects of exposures. Such systems must combine optimally universality (potential using for several toxic chemical compounds and in different regions) and specifity (potential using for analysis of a concrete situation), hard hierarchical structure (potential working of models in complex) and pliability (potential autonomous working of models and continuous improving of the system by adding of other models). The systems must be supplied sufficiently detailed input information and have the possibility to use results widely, in common with expert systems and/or decision-support systems on dyagnostics, prophylaxis, and treatment of poisonings, sanitary and hygiene, decontamination and so on.

Table.

Input/output information of CLEVER

Input data:
  Dose, mkg/kg/day
  Duration of exposure, days
  Application of dose (ingested/inhaled/percutaneous)

Output data:
  Coproporphyrin, mkg/day
  Uroporphyrin, mkg/day
  Delta-aminolevulinic acid, mg/day
  Erythrocytes, millions/ml
  Thrombocytes, thousands/ml
  Reticulocytes, %
  Haemoglobin, g/100 ml
  Bilirubin (direct/indirect), mg/100 ml
  Triglycerides, mg/100 ml
  SGPT (Serum glutamat-pyruvate transaminase), IE/100 ml
  Cholesterol, mg/100 ml

  Forecasting the incidence of chloracne
  Forecasting the incidence of porphyria cutanea tarda
  Forecasting the incidence of hyperceratosis
  Forecasting the incidence of increasing:
      spontaneous abortions
      prenatal death
      birth defects (cleft palate and so on)
  Forecasting the risk of liver malignant neoplasms
  Forecasting the risk of skin benignant neoplasms

     We think that the process of creating such model systems
may promote coordination of investigations. There are many
experiments whose interest, important results can't be used as
input information for mathematical models since the experiments
were not oriented on this primordially. Information needs of
objective, applied methodology of complex risk assessment are a
strong argument for more strict planning of experiments.
Results of these experiments will be valuable both for theory
and practice and for modeling. We consider that the possibility
of using such systems for creating banks of model situations is
very important. Early studying of character of development of
critical situations allows to improve both environmental
protection programs and the system itself.

RSK
Session 27

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