

US EPA ARCHIVE DOCUMENT

***"Challenge to improve the precision of Risk"
evaluation system for human" .***

*—specifically regarding the incorporation of
sufficient parameters*

chemical dynamics under environment and in the body



EPA-ICCA Biomonitoring Meeting

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Background, Issues and tasks to be solved, approach

- **JCIA's action plan and schedule**



ICCA's position on human Biomonitoring

- Support for the Appropriate Use of BM Information in Risk Assessment in Creating Public Policy
BM itself can not answer questions about risk or the safety of the substances
- Support for Appropriate Interpretation and communication of BM information to promote Risk-based Decision Making

Development & dissemination of chemical specific methods & information necessary to Interpret BM results & to promote risk based Decision-making

JCIA's interests



To develop more advanced and accurate Risk Assessment system for human



Apply the above system to support for **appropriate Interpretation** and communication of BM results.





Two sectional approach on chemical fate from the source to human

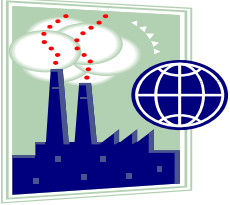
Approach 1

What's substance you have intake under the living environment or space?

These are “Origin” or “decomposed” chemicals?
with Biodegradation, hydrolysis or photo-degradation etc.

Approach 2

Which and How much substances you have retained in your body and are within safety level?
and it's Metabolites or conjugates ? Active or not ?



Approach 1

Two sectional approach on Chemicals Paradigm Environmental fate and ADME

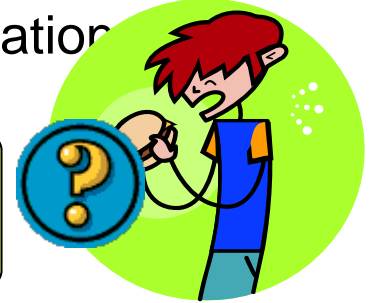
Degradation or Transformation under Environment

Approach 2

Intake via Oral, Dermal or Inhalation

Absorption

Which chemicals you intake?
Original or not?



Chemical in Blood

Distribution

Excretion

Chemical in Target tissue

How long and how much chemicals retain and tissues are exposed ?

C_{max} , $T_{1/2}$, and AUC_{0-48} etc.

Metabolism, Conjugation



Metabolites in tissue

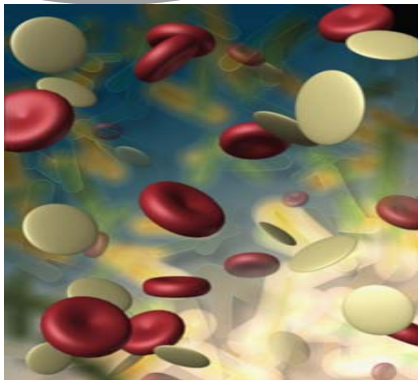


Metabolite in Blood

Excretion

Urine, Feces
Milk
Hair, Nails

Urine, Feces
Milk
Hair, Nails



Approach 1 Degradates-Prediction Methods for Environmental Chemicals

- A resting challenge for BM is how to implement BM of degradable and/or short half-life chemicals in the environment as well as humans.
- It is limited to experimentally determine degradates/metabolites of astronomical numbers of environmental chemicals, and what is required to develop their prediction methods.

The availability and practical approaches for prediction of degradates by,

1. **Photo degradation**: Critical degradation process for pesticides and high vapor-pressure chemicals, including electrophilic chemicals derived from photo oxidation of e.g., PAHs on ambient particulate matters (PM 2.5 -10 μ).



2. **Hydrolysis**: In many cases, an initial degradation process for environmental chemicals. And, knowledge-based data-collection is possible for many chemicals.

3. **Biodegradation**: Seems to be the most important process, and QSAR-based prediction methods have been developed by a NEDO/METI national project.

** Not a major scope of our*

survey.

Approach 1

Preliminarily findings and Conclusion

(Tentative)

- New computational tools for prediction of **photodegraded** and **hydrolyzed products** are required, in addition to those of biodegraded ones
- To date, **knowledge-based expert system is a feasible** one for this kind of prediction tool.
- **Establishment of qualified database is crucial** to enable the extraction of knowledge-based reaction rules and the analysis based on the data-mining.
- The database may subsequently promote the development of semi-empirical prediction methods and application of first-principle calculation, e.g., SPARC system (EPA) and GRRM (Prof. Ohno, Tohoku Univ., Japan), respectively

1. Database for Photo degradation and Hydrolysis

- Data format such as items and their description needs to be suitable for computational processing
- Required function, interface, and publication site etc should be carefully investigated.

2. Data extraction/mining from database

Need to be done by expert research team, not by a particular researcher

3. Degradates prediction system based on the extracted rules

Various conditions will be added on each extracted rule, so inter-rule dependencies, priorities and weighting need to be investigated and adjusted. The validation/test-run system is required. Through the validation run, user-required new parameters will be added, then more user-oriented system be constructed.

Approach 2

The Trial of Elaboration of Risk Evaluation *To develop more accurate risk assessment system*

Basic concept

- It's possible to use the results of animal studies to predict, **to a certain degree**, the estimated or total exposure level and exposure duration for specific substance in target organs and the blood in humans using currently available pharmacokinetic prediction methods, such as PBPK and/or TDTK models
- If this *“forward dosimetry approach”* can be **further refined**, more accurate risk assessment for humans could be attained from the relationship between toxicity and blood and target organ concentration levels from NOEL, NOAEL, or reference dose (RfD) etc. obtained from animal studies.
- In order to put this approach into practice, the following aspects from the perspective of **“Intra and/or Inter Species-species difference”** still need to be addressed

Is this “Pandora’s box?”



Approach 2

Two key issue in Advanced Risk Assessment

Approach

Existing Risk Assessment System

Tox./Hazardous Data (Repeated)



Out-put

NOEL,NOAEL and LOAEL Endpoints



Limited Toxicological Indices

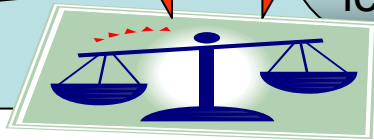


Margin of safety or UFs, are reasonable value?

RfC, RfD, ADI

DNEL Dermal
Oral
Inhalation

Exposure level



Human
Biomonitoring
Results

Safe or not?

Forward
Dosimetry

Forward
Dosimetry

BE:Blood, Serum,
Plasma level,Urine
level

How to
deliver the
levels from
dose level?
by PBPK or
Others?

Approach 2 *The Trial of Elaboration of Risk Evaluation*

Focused to develop Advanced Forward Dosimetry approach

Current/Traditional assessment system

NOEL,NOAEL  RfC, RfD,TDI etc



Safety factor

Safety level of exposure (estimated) in humans are determined or compared using values (RfC, RfD or TDI) that are derived with the treatment of NOEL and NOAEL with UFs safety index (species difference: rats→humans, interindividual difference), etc.

Key Issue: Above safety factor or indexes are reasonable value?

To elaborate PBPK model

PBPK/Extrapolation

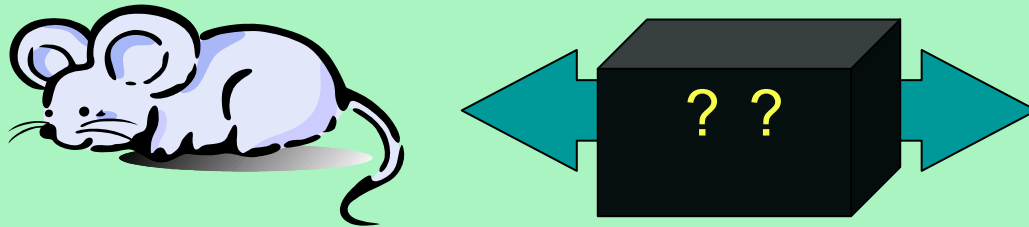
Pharmacokinetic approach using individual PBPK and TDTK models are essential. However, still remaining many issues.

Key issue: How could we establish appropriate PBPK model with introducing more precise index such as *In vitro* or *in silico* experimental parameters

Appendix 1

“Species (Intra and inter) species difference”

Essential issue of “Species (Intra and inter) species difference” still exists when extrapolating to humans the risk assessment from animal experiments, and this issue is frequently debated with regard to evaluating the adequacy of the safety factor in risk assessments and in the establishment of permissible exposure levels.



Appendix 2

Factors for Safety margin (MOE or others) in Traditional Risk Characterization

Extrapolation of mammalian data to human

Regulatory Benchmark : 100 ~ 1000

Safety Margin CF Composite Factor = 100

Base of safety factor, uncertainly?

Species difference (interspecies)	Individual difference (Intraspecies)	Additional Factor
10 0) = 100	× 10	× (3 - 1
Risks 1000 ?	10 ^{0.6}	Toxic Kinetics ~
Human	10 ^{0.4}	Toxico Dynamics

Aspects to be considered in Species Difference

- The transformation and absorption processes that the chemicals undergo in exposure to humans; (Almost same Physiologically base?)
- The actions of the chemicals in the body, especially their metabolism, rates of metabolism and elimination, and retention;
- Interactions of the chemicals with different organs and tissues (as mediated by receptors, by the level of lipid-solubility, or by antigen-antibody responses);
- The uniqueness of hormones, enzymes, and other physiological factors in humans; and the binding of the chemicals and serum proteins.

Further factor to be considered?

More complexity

In using prediction methods, including the PBPK model, for performing risk assessment in humans, factors such as changes in metabolic rates, due to the induction of hepatic and other enzymes on exposure of an individual to multiple chemicals, as well as age and sex differences, need to be considered.

Approach 2 Preliminarily findings and Conclusion

- Focus on the factors that are thought to be the most important in formulating these predictions system for RA or estimating BE including chemical metabolism, kinetics and species difference
- Some useful factor will be incorporated e.g. the data from *in vitro* and *in silico* into the previously used PBPK model or other tool to produce a further refined model.

Especially,

- To consider the introduction into our prediction model of parameters obtained from *in vitro* experimental results using human liver microsomes or the relevant enzyme system.

determination

PBPK models with a simple structure, approximately 10 parameters should be determined (CLH,int, CLR, Fa , fp , Ka , Psu , Vd , EC50 , etc.).

Possible
solution
idea

a. Collection and application of information from literatures as much as possible

b. Prediction of parameters from *in vitro* information

- Prediction of gastrointestinal absorption rate from the experiments using **Caco-2 cells**.
- Prediction of intrinsic hepatic clearance based on the data of **human liver microsomes**.

c. Prediction of parameters *in silico*

- Prediction of parameter values from physical properties such as hydrophobicity, number
- of Predictable of mass, by degree of target tissues.
- Prediction of volume of distribution.

d. Select parameters for which precision is required by sensitivity analysis

- The effect of parameter values on prediction values is to be cleared by sensitivity analysis. The key parameters should be determined carefully, while the parameters with low effect are to be determined by the appropriate method .

To accomplish our goal -----

Step by step approach on Scientific base with PDCA cycle

Approach 1

Plan and schedule for Degradates-Prediction System (Tentative)



Establishment of Database is Critical !!

1st year (Oct.2007-) : Investigate the design/specifications of database by expert, and create a prototype of database.



2nd year (Oct.2008-): Identify issues and re-investigate the design/specifications through the data extraction and input.



3rd year (Oct.2009) : Construct a first version of database, and limitedly open it to collect user's requests.

Approach 2

Plan and schedule for the Trial of Elaboration of Risk Evaluation

1st Year (June.2007-Dec.2007)

Survey the current status worldwide of the development of the database or systems, primarily those including PBPK/TDTK model, METEOR, BioFrontier/P450 etc.

2nd Year (Oct.2007-)

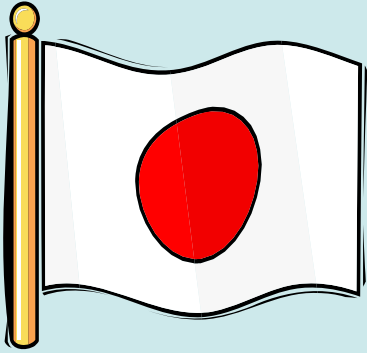
Extract the issues and challenges associated with use of the current model and or prediction system and to identify what or which field of approach are required . Including Experimental verification.

3rd Year (Oct.2008-)

Start to the full-scale research project to establish the system



Thank you for your attention!



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