2.2 Tier 2 models

Tier 2 models provide us a higher level of analysis on aggregate exposure assessment, deriving quantitative relations within the source to dose continuous. For this purpose, their design is based on the substances/regulatory purposes that need to be addressed and a there is a wide variability with regard to the individual sub-models included in each approach.

2.2.1 EUSES

European Union Directive 92/32/EC and European Commission Council Regulation 793/93 require the risk assessment of new and existing substances. Principles for this risk assessment have been detailed in a package of Technical Guidance Documents (Vermeire et al. 1997). The European Union System for the Evaluation of Substances (EUSES) has been developed as a result of collaboration between the European Commission, the European Chemical Industry and EU Member States. The development of EUSES has involved the adaptation and incorporation of the Dutch National Institute of Public Health and the Environment (RIVM) Uniform System for the Evaluation of Substances (USES) and the UK Health and Safety Executive Estimation and Assessment of Substance Exposure (EASE) models, in line with the Technical Guidance Documents. The EUSES model system aims to provide quantitative assessments of the risks posed by new and existing chemicals to man and the environment.

EUSES comprises 6 main modules (Lijzen 2004), as follows:

- Input module

- Release estimation module

- Environmental distribution module

- Exposure assessment module

- Effects module

- Risk characterization module

- Output module

which are graphically illustrated in Figure 2.

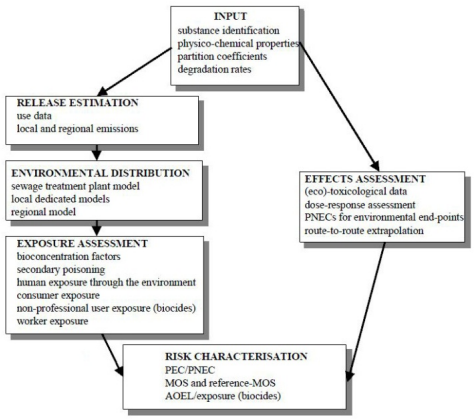

Figure 2: The main modules of EUSES (Lijzen 2004)

The main advantages-capabilities of EUSES arise from the fact that it has the ability to deal with a variety of different substances and initially requires relatively few input parameters (Fryer et al. 2004) .
On the other hand, some disadvantages of the model are that it adopts a conservative approach using reasonable worst case assumptions and default values, it is not designed to perform site-specific exposure assessments, it includes no method for incorporating variability and uncertainty into exposure assessments, while the chemical applicability of the system has been found to be limited. An additional drawback is that EUSES links the overall uptake to probable health endpoints through exposure/response relations without taking into account the toxicokinetics/toxicodynamics and the related internal dose and, thus its several modules are not equally refined.

2.2.2 Calendex

Calendex™ is a software system developed by Durango Software and licensed through Novigen Sciences, Inc. and is a proprietary product available under license. Access to the underlying algorithms, data structures, operations of the probabilistic functions and other key elements of the model are not available to non-license holders. The system provides estimates of exposures that are statistically representative of the U.S. population that occur from pesticide residues in food, in the home, and in tapwater through a variety of possible exposure pathways. Calendex™ has a two-part structure, the first being the dietary analysis module, DEEM™ and the second part constructed to calculate the non-dietary component of the aggregate and risk (Price 2001)
.

Calendex™ is an activity based modelling approach, that takes into account the variety of activities that contribute to the overall uptake of the selected contaminants from a selected population sample. Exposure distributions for the targeted populations (probabilistic assessments) are derived by specifying the input variables as distributions rather than as single values and a Monte Carlo simulation technique is adopted (DURANGO 2010).

Calendex is considered to be a robust scientific tool for assessing aggregate and cumulative exposures and risks to human health for deterministic as well as probabilistic assessments. However, due to the demand of detailed input data, it is difficult for use by non-professional experts and its applicability is limited to pesticides. Moreover, a direct application to EU populations exposure assessments would not be very representative, since its development was fully based on US demographic data.

2.2.3 CARES

CARES™ (Communities Actively Research Exposure Study) is developed by the American Crop Protection Association with input from a variety of stakeholders. The purpose of the software is to determine aggregate risks from drinking water, residential and dietary exposure for a single pesticide and cumulative risks from pesticides that have a similar mechanism of toxicity (Price 2001). CARES utilizes concepts from existing exposure and risk assessment software either under review or already being used by US EPA (CropLife 2002)
.

The CARES model quantifies risks to human health from exposures to pesticides trough several possible exposure pathways and in a variety of temporal resolution within a limit of one year (Fr yer et al. 2004)
.

A major difference to Calendex, is that individuals assessment is not based on the activity pattern of each individual; instead an upper risk boundary estimation is conducted, while probab ilistic assessments adopt for once more a Monte Carlo simulation technique, based on the distributions of exposure factors of the wider population.
(Baugher et al. 1999)
.

2.2.4 LifeLine

The LifeLine Group at the Hampshire Research Institute, USA, has developed the LifeLineTM model to estimate single, aggregate, and cumulative exposures and the qoncequetive risks to pesticides for US consumers. The model acts as a tool to support regulatory decision making under the 1996 Food Quality Protection Act (Hampshire 2002).

LifeLine™ follows a similar approach to Calendex for assessing individuals exposure, based on detailed daily food consumption dat, which are existing from the Continuing Survey of Food Intake by Individuals (CSFII, 1989-91, 1994-96 and 1998) for several age groups and ears of the season as much as information on pesticide residue levels in raw agricultural commodities. For different pathways, pesticides concentrations in tap water, but possible exposure pathways through ambient air are not taken into account, a fact that is one of the main drawbacks of the model, limiting its applicability for in house aggregate assessments. However, probabilistic assessments are also feasible, in a similar manner to the previous models.

2.25 ConsExpo

The ConsExpo model system has been developed by the National Institute of Public Health and the Environment (RIVM), Netherlands, in order to assess human exposure to and uptake of chemicals used in consumer products, and some of the exposure algorithms included in ConsExpo (Vermeire et al. 1993) have been adopted as part of the European Union System for the Evaluation of Substances (EUSES).

CONSEXPO is based on a modeling framework developed by Van Veen (Van Veen 1995, 1996) to evaluate contact, exposure and uptake of chemicals emitted by consumer products (but only for non-professional use). The model contains an extensive database of consumer products use and chemical properties and a set of models for assessing exposure and uptake from several exposure pathways. Exposure analysis includes a variety of temporal resolution, as much as deterministic and probabilistic assessment tools. However, its use is limited to consumer products and as such it does describe risks for environmental contaminants and the related contribution contaminants both present in the environment and in consumer products. Moreover, no link from exposure to internal dose is provided.

2.2.6 SHEDS

The Stochastic Human Exposure and Dose Simulation (SHEDS) models have been developed for the US Environmental Protection Agency National Exposure Research Laboratory's Office of Research and Development. SHEDS forms part of their research programme to develop probabilistic human exposure source-to-dose models (HES2D) that estimate multimedia and multi-pathway pollutant exposures of general as well as at risk populations (Price 2001) for estimating exposures to pesticides and particulate matter respectively.

The SHEDS approach for assessing individuals exposure is based on a concept similar to Calendex expanded to take into account time-location-activity diaries contained in the Environmental Protection Agency's Consolidated Human Activity Database (Zartarian et al. 2002) and all possible exposure pathways, such as non-dietary ingestion exposures from hand-to-mouth and object-to-mouth.

An additional advantage to the previous models is the fact that a two-stage Monte Carlo solution technique is used for assessing population exposure, allowing thus variability and uncertainty to be characterized separately. Moreover, it estimates metabolites concentrations in urine and blood by using simple pharmacokinetic algorithms (not PBPK models) and allowing some

interpretation to biomonitoring data.

2.2.7 MENTOR

To improve the exposure assessment approach further, the methodology first developed for the SHEDS model was modified and incorporated through new, generalized code into the Modeling ENvironment for TOtal Risk studies (MENTOR) (Georgopoulos et al. 2006a; Georgopoulos et al. 2006b; Georgopoulos et al. 2005; Lioy et al. 2007)
, which was designed to analyze not only exposures to individual contaminants but to assess physiologically based target tissue dose of Multiple co-occurring contaminants via Multimedia, Multipathway, Multiroute exposures (4M) for specific individuals or for study-specific populations. A conceptual description of the model is presented in Figure 3. MENTOR-4M (Georgopoulos et al. 2008)
, in addition to addressing the issue of simultaneous exposures to multiple contaminants for any specific individual within the population of concern, provided a newer, enhanced framework of source-to-dose analyses, as it allowed calculations of tissue specific dose (and corresponding biomarker levels), employing Physiologically Based Pharmacokinetic (PBPK) modeling. Under this perspective, MENTOR is not considered as a single model; it is an evolving, open, environment for supporting consistent multiscale source-to-dose modeling for human exposures to contaminants.

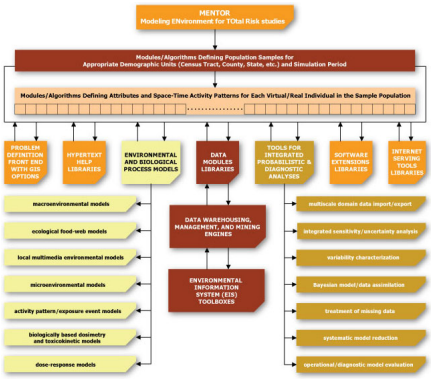

Figure 3 MENTOR conceptual representation

MENTOR has a strong orientation towards the exposure that occurs as a result of the movement of contaminants in the environment (national and region air quality, local air quality, widespread or localized contamination ground water.) However, the model framework could be applied to any source of contaminant. The MENTOR approach lends itself to compartmental and mechanistic based models of exposure. These approaches can be based on either macro or micro-activity approaches (Figure 4).

Figure 4: Microenvironmental exposure-dose modelling system (Georgopoulos 2008)

The major advantages of MENTOR are related to the fact that the source to dose continuum is described with a full mechanistic approach and internal dose modeling is implemented, meaning that aggregation of exposure can be done at the biologically effective dose level. This allows the easy interpretation of human biomonitoring data for exposure and risk assessment. Moreover, exposure reconstruction through biomonitoring data seems feasible, providing additional links on policy implications on the exposure determinants. The main drawback of MENTOR-4M is that it is extremely data intensive, thus its application is still limited to a few substances only.

2.2.8 Concluding remarks

By definition aggregate exposure assessment in the highest Tier requires all possible exposure pathways from source to dose to be taken into account. Although contamination could be roughly differentiated in environmental-originated (pesticides, traffic pollutants, indoor materials) and consumer products-originated, a more comprehensive overview reveals that the overall frame is more complicated; there are contaminants both present in environment and consumer products, as well as many consumer products contaminants they end up to the environment entering in a related process of media transfer-transformation.

Most of the models reviewed above were developed in order to tackle specific regulatory needs. Consequently they have methodological limitations due to their initial scope. Thus, the following pitfalls might be observed:

- lack of specific pathways

- lack of a variety of substances

- lack of equal level of development among the several stages of the assessment

It also worth mentioning that only SHEDS implements some pharmacokinetic relations for assessing metabolites in key biological fluids, while only MENTOR has the capability to assess internal dose and derive the biologically effective dose of the substance at the target tissue(s), as well as provide a facility for biomonitoring data interpretation. Beside internal dose modelling, the overall approach of MENTOR is by far the more comprehensive, considering that the most elaborated models are used in each stage of the source to dose assessment. In this context it is reasonable that at the current stage of development a limited number (but a large variety) of contaminants were tackled.