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Exposure Assessment in the Context of the EU Technical Guidance Documents on Risk Assessment of Substances

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SUMMARY

The ECETOC Task Force "Exposure Modelling" critically reviewed the EU Technical Guidance Document for Risk Assessment of New and Existing Substances and identified a number of specific exposure assessment issues which may require further consideration. These are described in this Document No. 35 which should be viewed as a status report. It should enable ECETOC to further prioritise activities in the area of exposure and risk assessment, which would form the basis for the further collaboration with the national competent authorities on the development of a mutually agreed risk assessment system in support of EU legislation. Although the basic principles of European risk assessment are scientifically sound and mutually accepted, the Technical Guidance Document in its present status of development often only allows risk assessments which are too generic and too conservative. Consequently, many details will need to be developed in order to tailor the risk assessment process more to the specific needs.

In several of its Technical Reports, ECETOC recommended that before proceeding with a risk assessment, the assessor should establish whether exposure of man or the ecosystem to the substance of concern is likely to occur. If so, a process for assessing environmental and human health-related exposure must be employed to enable a risk assessment to be carried out. This process is a practical step-wise risk assessment procedure which essentially consists of an iterative comparison of exposure to effects. Although the EU adopted the step-wise risk assessment approach, the Task Force concluded that in particular Tier 1 (or screening phase) of the risk assessment process fails to separate out those substances which are of no concern. Tier 1 needs to be designed to be sufficiently selective, so that substances of real concern can be identified, and these concerns addressed, quickly and efficiently. The Task Force also concluded that the current system or process as detailed in the Technical Guidance Documents is over-conservative and may lead to a large amount of unnecessary testing.

For both human and ecological risk assessments, a large number of factors and often complex pathways need to be considered when estimating exposure. For both assessments, a worst case analysis (maximum possible exposure) should be used only as a screening tool to establish whether exposure can be categorised as "insignificant" and not as the basis for predicting actual human or environmental exposure. Sole use of the worst case approach leads to an unrealistic characterisation of exposure conditions and merely expresses the precautionary principle rather than the facts.

Assessments should move from 'risk characterisation' by means of PEC/PNEC comparisons to 'risk estimation', i.e. the quantification of the likelihood of the incidence and severity of adverse effects, characterised in terms of a statistical distribution with a most probable value for the risk and some confidence interval and not by a single number. ECETOC has started a project entitled 'ECIMOS' with

the objective to develop an Integrated Modelling System or common modelling platform for exposure, effect and risk modelling using existing model algorithms or calculation modules which integrate state-of-the-art methods for sensitivity and uncertainty analysis for different aspects in the exposure, effect and risk assessment of chemical substances.

1. INTRODUCTION

The goal of a comprehensive risk assessment is to estimate the likelihood and the extent of an adverse effect occurring in man, animals or ecological systems from possible exposure(s) to substances or physical agents. The assessment of whether a substance presents a risk to the receiving environmental compartment is based on a comparison of the Predicted (or measured) Environmental Concentration (PEC) of the substance of concern with the Predicted No-Effect Concentration (PNEC) to organisms in that ecosystem. The assessment of whether a substance presents a risk to man is based on a comparison of the predicted (or measured) exposure for a human population of concern with a No-Observed Adverse Effect Level (NOAEL), generally derived from experimental animal studies.

Mathematical models have been developed as decision-support instruments for risk assessors which facilitate the performance of calculations, e.g. USES (RIVM, VROM, WVC, 1994) or HAZCHEM (ECETOC, 1994a). The development of the Technical Guidance Document for EU Risk Assessment of New and Existing Substances calls for a model which mimics the Document in every detail. Therefore, a European working group was established in 1994 with the aim of developing a "European Union System for the Evaluation of Substances" (EUSES).

To further explore when and how exposure assessment procedures and methods should be revised and improved, the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) formed a Task Force in 1994 with the following Terms of Reference:

- review in detail the USES model and identify elements needing modification and further development;
- develop proposals for an updated version (EUSES) which are in accordance with the concepts developed by ECETOC;
- define the applicability of EUSES to each tier of the risk assessment process;
- collaborate with the national competent authorities on the development of a mutually agreed risk assessment system in support of EU legislation;
- develop a data base for environmental parameters to be used in generic regional and local situations.

This Task Force carefully observed the EU activities of merging the Technical Guidance Documents for risk assessment of new notified substances with those of existing substances and provided input via the technical EU working groups at various stages of the process. The Task Force critically reviewed the assumptions and equations used to predict *exposure* to substances within the European risk assessment, and recommended some practical approaches to improve critical aspects within the environmental, consumer and occupational exposure assessment methodology. In addition, representatives of the Task Force participated in two EU Special Expert Meetings which were held in The Hague, NL, one on Biodegradation (31.5.-1.6.1995), the other on Release Estimation (19.-21.9.1995).

The Task Force also supported actively the development and testing of EUSES, the model based on the algorithms and tables provided in the new "Technical Guidance Documents in Support of Directive 93/67/EEC on Risk Assessment of New Notified Substances and Regulation (EC) No. 1488/94 on Risk Assessment of Existing Substances" (EEC, 1996).

This Document No. 35 was prepared for information of ECETOC member companies, particularly those which were not closely involved in the development of the Technical Guidance Documents for new and for existing substances and the subsequent merging process of the two documents. It will therefore focus on the critical assumptions used for the estimation of environmental, consumer and occupational exposure as described and recommended within the present EU Technical Guidance Documents. Underlying processes and mechanisms will be reviewed and suggestions will be made for improvements by the incorporation of recent scientific developments.

2. BACKGROUND

2.1 NEW CHEMICAL NOTIFICATIONS AND RISK ASSESSMENTS

Since 31 October 1993 all new chemicals notified to the EU authorities must comply with the 7th Amendment of the Dangerous Substances Directive 67/548/EEC (EEC, 1992). This implies that competent authorities are required to conduct a risk assessment for man and the environment for the chemical being notified according to the principles laid down in the Commission Directive on Risk Assessment of New Chemicals (93/67/EEC) which was published in the Official Journal and came into force on 31 October 1993, i.e. the same day as the implementation of the 7th Amendment of Directive 67/548/EEC.

The results of the risk assessment at each stage of the notification will form the basis for risk management decisions (e.g. no immediate concern, further testing at higher tonnage triggers, immediate further testing or risk reduction). As tonnage and/or use patterns change, the risk assessment must be revised and where a concern is identified, the competent authority is empowered to request additional data from the notifier (toxicity/ecotoxicity data or exposure data).

Although the time period for gaining experience has been relatively short, industry is finding that the different Member States are approaching the risk assessment requirement quite differently. Clearly, the sophistication of the risk assessment seems to depend on the resources available within the competent authority for handling a variety of data. Some authorities see the 7th Amendment as a tool for requesting further data in each case while others prefer to use the opportunity to better understand the potential risks in collaboration with industry.

2.2 EXISTING CHEMICAL SUBMISSIONS AND RISK ASSESSMENTS

Article 10(4) of the Council Regulation (EEC) No. 793/93 on the Evaluation and Control of the Risks of Existing Substances requires that a risk assessment be carried out according to principles later described in Commission Regulation (EC) No. 1488/94 for Risk Assessment of Existing Substances (1488/94/EEC).

The Council Regulation requires that dossiers be submitted on existing substances (i.e. those listed in the EINECS Inventory which contains about 100,000 substances) exceeding certain defined production volumes per year. All data pertaining to the ecotoxicological, toxicological and physico-chemical properties of the substance are collected in the format of the Harmonised Electronic Data Set (HEDSET) and will be included in the database IUCLID developed by the European Commission.

In accordance with Regulation 793/93, Phases I and II of the HEDSET submissions have been completed by industry in Summer 1995 for about 2,500 "high tonnage" existing substances (those produced or imported in quantities exceeding 1,000 t per year) in accordance with two official deadlines (4 June 1994 and 5 June 1995, respectively). These datasets were loaded into the IUCLID database of the European Chemicals Bureau (ECB) in Ispra, Italy. Copies of these data files were immediately given to the competent authorities of all EU member states for loading into their own IUCLID systems. In May 1996 the *non-confidential* parts of the *merged* datasets were made available by ECB to all interested parties (industry, consumer groups etc.). "Merged" means that datasets for one substance received from different submitters were combined. "Non-confidential" means that confidential data like production volume as well as data flagged as confidential by the submitter were removed. These datasets can be purchased on CD-ROM with IUCLID export files or as a so called "IUCLID low cost version" for those not having a IUCLID database. The IUCLID low cost version is a CD-ROM-based document retrieval system for searching IUCLID reports by name, CAS or EINECS Number but does not have the functionality of a database.

The final HEDSET submissions - Phase III - required for all other chemicals produced or imported in quantities exceeding 10 t per year must be completed by industry on 4 June 1998.

Using the IUCLID data bank, the EU and Member States will draw up priority lists of about 50 chemicals per year for risk assessment by the regulatory authorities. In principle, the submitted substance data will be used to rank the substances according to their relative risk based on an automated Informal Priority Setting method (IPS). Substances which have been prioritised will then be evaluated and assessed according to the principles laid down in the Risk Assessment Regulation.

The first priority list was published in May '94 and contained 42 substances. Several member states are preparing risk assessments on these priority substances. Recently, about 10 *draft* risk assessments were made available and were discussed during a Technical Meeting. The second priority list was published in September 1995. EU member states including the "new" member states can already begin the risk assessments for these substances, concurrent with the assessments of the first list. The second list contains 36 substances. A third priority list has been discussed and will be published soon in the Official Journal.

2.3 TECHNICAL GUIDANCE DOCUMENTS ON RISK ASSESSMENT

These documents are to provide harmonised guidance to all member state authorities on the procedures for conducting acceptable risk assessments for man and the environment. They are not legally binding but the intention and expectation is that European regulators charged with conducting a

risk assessment will use these documents for developing their conclusions concerning the potential risks of a chemical.

Since the introduction of risk assessment legislation in the EU, separate Technical Guidance Documents (TGD) have been prepared for the evaluation of both 'New' and 'Existing' Chemicals (EEC, 1993; 1994). Additional guidance documents were also developed on the use of QSARs (quantitative structure activity relationships) and on risk reduction and risk/benefit considerations.

The two sets of TGD for New and for Existing Substances respectively, were diverging in essential parts and hence could result in different risk assessment conclusions and consequently to different risk management strategies. Recognising this, the Commission decided to set up EU working groups in order to develop a uniform and consistent guidance package for new and existing substances. This harmonised guidance package for a comprehensive risk assessment of both new and existing substances was agreed on 8/9 November 1995 and published in 1996 (EEC, 1996).

Unfortunately, various changes were made during the amalgamation process which increased the conservatism of the risk assessment approach; new data were often not sufficiently considered and arguments were often not supported by solid science and/or peer reviewed literature. In addition, some controversial areas were not addressed with the probable result that the individual member states may conduct the risk assessment following their own national policies. Adoption of different risk assessment methods, assumptions and safety factors to produce so-called unique and 'precise' risk quotients will result in divergent "risk" conclusions, and is expected to lead to an inefficient use of available resources - within both competent authorities as well as industry.

3. RELEASE ESTIMATION

3.1 EMISSIONS

Estimating Releases or 'emissions' is one of the most important and also contentious areas of environmental risk assessment. This is the step that determines just how much of a substance actually enters the environment. In the TGD, various life-stages of a substance are identified, each of which may have its own associated release to the environment. These life-stages are production, formulation, processing (or use), recovery and disposal. For most substances the first three of these are usually considered and may or may not be significant in terms of the quantity released to the environment.

This information on releases is often difficult to obtain, particularly for the use or processing stage of a chemical's lifecycle, and different amounts and quality of release data are available for different types of substances.

In order to allow for this variability, a hierarchy of data type is given in the TGD, i.e. in order of priority:

1. specific information;

2. the emission scenarios as given in the TGD;

3. the estimated release factors from the release tables.

This hierarchy was agreed by both ECETOC and competent authorities and although there is overlap, the principle of the approach is sound. The new EUSES release module also reflects this and includes the basic 'flexible' approach proposed by ECETOC.

The greatest concern here is the interpretation of 'specific information'. The information to be considered may include measured release data or any factors that might affect the actual release to the environment. For example, the plant technology may use wet or dry processes in open or closed systems and these may be the main factors controlling the release to the environment. In addition, the number and location of production sites, number of days for emission etc. may be known, and this type of information should be used wherever possible to estimate the release. Therefore, 'specific information' should not be restricted to 'measured concentration values' and may include a combination of measured and estimated values.

When such specific release data are not available, it may be possible to utilise one of the 'emission scenario documents' referred to in the TGD. These documents identify typical release patterns for certain industry types (e.g. paints and varnishes, plastic additives etc.). The idea is that if it is known that a substance is used as a preservative in paints, for example, it should be possible to identify the pattern of release based on the pattern of production, formulation and use of paints which is provided in the document. Thus the emission scenario documents potentially provide a useful method to estimate release fractions.

However, it should be recognised that these emission scenario documents are based on varying degrees of information about the industries they represent and still only provide estimates of releases which may or may not reflect true release patterns. They usually do not take into account the state of technique used in manufacturing (e.g. BAT or dedicated units for mitigating releases) but assume conservative release figures. This will need to be corrected as more specific information becomes available. They also mostly fail to address the potential correlation between the sizes of the effluent stream and the receiving water. Further data collection is needed in the EU to substantiate such correlations.

The third option is to use the release tables provided in the TGD. However, this must be seen as a last resort when no other information is available. It should be emphasised that the release factors given in the TGD are not based on real release information and are deliberately conservative. Moreover, nearly all the recent industry assessments for priority list substances indicate that actual emission fractions, at least during production, are significantly lower than the fractions given in the release tables. For information, the default release fraction for existing substances (>1,000 t per year) at production and formulation is set at 0.3% release to wastewater, based on data provided by ECETOC for intermediates. For new substances the corresponding value for exposure assessment at base set (<10 t per year) is 2%, based largely on the experience of the UK Department of Environment. This 2% release value was made conservative in order to encourage industry to provide more specific information.

In terms of actual use, the different categories (industry/use/main) can be difficult to interpret, and it is not clear how these different categories might interact. There may be several use or industry categories that are applicable for one substance. Moreover, the release tables seem to be principally focused on the industrial categories, while the use categories are only taken into account to a lesser extent. Also, the current tables rely heavily on the influence of vapour pressure and water solubility for estimating the release during production, whereas recent investigations (ECETOC, 1994b) demonstrate that for intermediates there is, in practice, no such correlation between the properties of a substance and its release to the environment. Instead, the release is controlled primarily by the type of manufacturing or formulating process being used. It is essential that the user should be aware of these limitations when using the release tables.

3.2 CALCULATION OF $PEC_{regional}$

In environmental risk assessment, the Predicted Environmental Concentration (PEC) is used as a descriptor for the real environmental concentration of a given substance. While PEC_{local} characterises the concentration in the immediate vicinity of a point source, the $PEC_{regional}$ reflects the background concentration in areas not directly affected by point source discharges. There is an important difference which strongly influences the methodology to be applied in determining these values.

In the case of PEC_{local}, the concentration is always related to the strength of the point source and the various fate processes (e.g. advection, degradation) which can be measured and quantified. Hence the resulting concentration in the vicinity of a point source can be predicted by using an appropriate local model. The results of the model predictions can be scrutinised, provided that the analytical methodology is available.

With increasing distance from the point source, fate processes and contributions from other sources will become more important. In situations where no direct influence from point sources occurs, a steady-state concentration of a substance in the different environmental compartments is assumed. These steady-state concentrations, calculated by the fugacity approach, represent the $PEC_{regional}$ or background concentration. Analytical measurements in the environmental compartments concerned are generally feasible. Since the concentrations depend on the fate and release processes, the $PEC_{regional}$ may vary considerably in reality. Therefore, a stochastic approach could improve the estimation of the $PEC_{regional}$.

4. BIODEGRADATION

4.1 INTRODUCTION

The PEC may significantly be reduced by biological and/or physico-chemical processes and as a consequence may result in a reduction of the PEC/PNEC ratio. For most of the substances for which an exposure assessment has to be executed, the biological degradation processes are most important, particularly because the PEC/PNEC comparisons are based on the parent substance. Biodegradation (kinetics) and exposure predictions should therefore be related to primary biodegradation. In addition, it is important to acknowledge and accommodate the hierarchy in test results. In principle, should monitoring data for the chemical of interest be available, based on specific analytical measurement of the substance itself in an effluent under actual field conditions, then these data should take precedence over laboratory simulation tests and/or model predictions. Different approaches could be used for the interpretation and use of test results; knowledge gained on the extrapolation of results from laboratory tests to the field should be used to predict the fate and behaviour of the substance. It is therefore essential to clearly distinguish 1) use of expert judgement or simple calculation algorithms, 2) 'direct' extrapolation of biodegradation test results and 3) use of mathematical models which simulate competing fate processes and operations of Waste Water Treatment Plants (WWTPs) and other environmental compartments (river, soil).

4.2 PRIMARY, READY, AND INHERENT BIODEGRADATION

Mathematical models currently in use to predict environmental concentrations of substances also require knowledge of the kinetics of biodegradation. Ideally, the measurement of primary biodegradation requires specific analytical methods which are sensitive enough to determine concentrations relevant to the environmental compartment of concern. Such methods could well be difficult to develop within a reasonable period of time and it is therefore often necessary to assess primary degradation based on tests using non-specific methods.

Within the current framework of legislative test methodology, the methods for assessing ready biodegradability usually provide the only biodegradation information available at the base set level. These ready biodegradability tests may provide an indication of the completeness or extent of ultimate biodegradation of the substance, but do not always provide a good basis for the calculation of primary biodegradation rates. It is generally accepted that compounds meeting the "ready" criteria are totally mineralised and their biodegradation rates are fast enough to achieve a high removal in WWTPs.

A substance which cannot be classified as "readily" biodegradable but can be shown to be susceptible to microbial attack is defined as "inherently" biodegradable. Testing for inherent biodegradability can be performed by means of one of the three OECD Guideline methods, i.e. SCAS, Zahn/Wellens, MITI II (OECD, 1992). The first two tests measure removal, including biodegradation but also adsorption. Tests in this category have been designed to have very high biodegradation potential. For substances which do not degrade under conditions of inherent tests it is assumed that under environmental conditions biodegradation rates may be insufficient to significantly reduce exposure within the residence time. Inherent tests may sometimes overestimate the removal due to biodegradation in environmental compartments - even in WWTPs - due to the infinite sludge retention times. The test results should therefore be used with care for predictions of biodegradation kinetics for environmental compartments.

Suitable laboratory techniques exist for simulating activated sludge sewage treatment which can provide accurate predictions of the behaviour of substances in this process. In addition, the kinetics of biodegradation can be studied directly and the effects of variation in operating conditions can be assessed. There are also good simulation tests that only need non-specific (TOC) analyses such as a SCAS test with fixed SRT (van Ginkel *et al*, 1995).

4.3 BIODEGRADATION IN THE CONTEXT OF THE EU TGD

Although competent national authorities agree that most of the ready biodegradation tests that are used at the moment are aimed at measuring the mineralisation of a chemical rather than primary biodegradation rates, European and national resources and efforts have been primarily focused on the potential use of the current test methods for risk assessment, rather than on the development on new alternative test methods.

Therefore, in order to make use of the existing biodegradation test results and the biodegradation testing that is requested in the present EU chemical legislation, competent national authorities have proposed to assign rate constants to the results of the standard tests that can be used in WWTP models, river models, soil models and Mackay level-III models. These rate constants, which are presented in Table 1, are based on a limited number of empirical data and are generally extremely conservative for most ready or inherently biodegradable substances.

Table 1: Elimination in WWTPs as proposed in the TGD: Extrapolation from test results to rate constants in a WWTP model (SimpleTreat)

Test result	Rate constant k (h^{-1})	WWTP Removal (%)
Ready biodegradable	1	91
Ready, but failing 10-day window	0.3	75
Inherently biodegradable, fulfilling specific criteria	0.1	50
Inherently biodegradable, not fulfilling specific criteria	0	0
Not biodegradable	0	0

4.3.1 Biodegradation in Waste Water Treatment Plants (WWTP)

The TGD refer to the model SimpleTreat (Struijs *et al,* 1991) to predict removal in waste water treatment plants. SimpleTreat originally used a rate constant of 3 $hour^{-1}$ which was rather arbitrarily reduced to 1 $hour^{-1}$ during the amalgamation of the TGD and is consequently extremely conservative. In practice the model will only allow a maximum of 91% removal at screening level vs. 97% removal due to biodegradation using the original rate constants of Struijs *et al* (1991). For many substances, however, much higher removals are observed due to biodegradation, adsorption and volatilisation (Struijs *et al*, 1991), sometimes reducing the amount released to the environment by a factor of 10 or more.

Particularly for high tonnage chemicals with wide dispersive use it can be very important to accurately predict the removal in waste water treatment plants, and the SimpleTreat tables in the TGD (Appendix 2) are simply inadequate.

Instead of using simple elimination factors or recommending a default mathematical model to predict the material's fate during treatment, it is recommended to broaden the scope of waste water treatment plant models.

1. The goal of any model formulation is to account for the fate and distribution processes in a waste water treatment plant and to predict the concentration of substance in effluent, sludge and air. Readily biodegradable substances are assumed to biodegrade in aerobic waste water treatment plants. The Task Force came to the conclusion that the current SimpleTreat approach as proposed in the TGD has severe limitations, and that the mechanistic formulations need to be further improved to account for the observations that:

    - sludge retention time is an essential parameter in determining the concentration in the effluent;

- effluent concentrations are independent of influent concentrations;
- adsorbed fraction in a biological aerator is available for biodegradation.

2. To accommodate the parameterisation of SimpleTreat - as a function of the available data in the base-set and HEDSET - default pseudo-first order rate constants have been assigned to readily and inherently biodegradable substances which are arbitrary, non-scientific and non-justified. In addition, it must be pointed out that by doing so the effluent concentrations at high influent concentrations are often overestimated, while at low influent concentrations they may be underestimated.

3. It is proposed to extend the model options with a predictive model formulation based on Monod kinetics. This implies that the assumption of microbial growth is introduced. This model approach assumes that the effluent concentration is independent of influent at steady state, and that the effluent concentration is a function of the maximum growth rate and the sludge retention time (SRT) Several formulations and approaches are available (e.g. ECETOC, 1994b). Steady-state conditions with continuous release scenarios are assumed. Discontinuous or intermittent release scenarios will need further elaboration with dynamic model formulation. The generic scenario is based on the presence of a continuous well-mixed biological aerator, with or without the presence of a primary settler. The operating conditions are pre-set on an agreed sludge retention time which should represent the median waste water operating conditions in Europe. It must be noted that the completely mixed reactor design represents a realistic worst case as compared to, for instance, plug-flow reactors.

4. It is proposed to develop tests, preferably based on existing ones, that produce key parameters for WWTP modelling purposes. The essential parameter needed for the Monod model is μ_{max}, for which an approximated worst-case value can be estimated from batch tests (e.g. Blok 1994, Grady *et al,* 1996). For the Ks value in this model a fixed value of 0.5 mgl^{-1} seems to be acceptable (Struijs, 1996).

   Similarly to the other WWTP models - if no biodegradation is observed in the ready test, and no information on inherent biodegradability is available, the concentration in effluent would be assumed to be equal to influent, and removal due to sorption and volatilisation should be accounted for assuming a liquor concentration equal to influent concentration.

Recent discussions of ECETOC representatives with the National competent authorities have resulted in a revision of SimpleTreat (Struijs, 1996) to incorporate greater flexibility and this will be included in the new EUSES model.

4.3.2 Biodegradation in Surface Water, Sediment and Soil

In the TGD, the rate of biodegradation in surface water, soil and sediment is assumed to be related to the structure of chemicals, microbial numbers, organic carbon content and temperature. The kinetics of biodegradation are assumed to be pseudo-first order, and only the dissolved portion of the chemical to be available for biodegradation. Thus biodegradation becomes dependent on the sorption coefficient Kd - which correlates to the log Kow. Similar to biodegradation in waste water treatment plants, the TGD provides tables of rate constants for surface water and sediments. These tables are derived from limited data from laboratory tests and extrapolated using empirical scaling factors. This approach which lacks a scientific basis was criticised because there is no evidence that (1) the first order rate constant k is proportional to the population density of micro-organisms in aerobic water, and that (2) degradation of chemicals takes place in the water phase only. It is suggested by the Task Force to develop an empirical database which relates measured biodegradation rate constants to pass/fail results of both ready and inherent biodegradation tests.

Biodegradation in the environment is determined by a variety of conditions For a given substance environmental half-lives may differ locally by orders of magnitude depending mainly on temperature, humidity and the micro-organisms available. Other than in a WWTP, however, there is no time limit for the exposure to the degrading factors. Because of the fact that degradation continues, although at various rates, there is less need to be conservative in estimating the degradation half-lives. The estimation of generic degradation half-lives appears to be sufficient which can be derived from experiments reflecting both the inherent degradation potential of the substance and the variability of environmental conditions. For readily biodegradable substances these generic half-lives must be considerably shorter than for inherently degradable substances, but even substances which fail the OECD inherent biodegradation test criteria show measurable half-lives in simulation tests on biodegradation in soil in most cases. For example, some pesticides showed half-lives of <10 d in simulation tests in soil or water/sediment even if the CO_2 formation during the test was small.

Therefore the half-lives given in the TGDs for inherently biodegradable substances of 150 d in water, ≥300 d in soil and ≥3000 d in sediment are probably extremely conservative as the following example highlights. Most pesticides are inherently biodegradable. If the above half-lives were real, such substances would have to be excluded from notification as pesticides for reasons of persistency.

There is a general lack of data on extrapolation of screening test results from laboratory to the real environment and therefore an urgent need to derive realistic default values for biodegradation rates in the environment, particularly soil and sediment. Data could be generated e.g. by correlating half-lives derived from simulation tests (e.g. for pesticides) with results of OECD degradation tests.

5. BIOACCUMULATION

A strategy for the assessment of the occurrence of secondary poisoning has been proposed within the EU TGD to support the decision when to request a bioaccumulation test. This strategy takes account of the PEC_{water}, the resulting concentration in food of higher organisms and the mammalian toxicity of the chemical as an indication of possible effects on birds and mammals in the environment via the food-chain.

The first step in the scheme is to consider whether there are indications for bioaccumulation potential. According to the EU TGD there is an indication, if

- at base-set level, a substance has a log $K_{ow} \geq 3$; *or*
- is highly adsorptive; *or*
- belongs to a class of substances known to have a potential to accumulate in living organisms; *or*
- there are indications from the chemical structure;
- *and* there are no mitigating properties, e.g. hydrolysis or ready biodegradability.

Subsequently, it is necessary to consider whether the substance has certain classifications on the basis of its mammalian toxicity data, i.e. the classification Very Toxic (T+) or Toxic (T), the classification harmful (Xn) with at least one of the risk phrases R47 'May cause birth defects', R48 'Danger of serious damage to health by prolonged exposure', R60 'May impair fertility', R61 'May cause harm to the unborn child', R62 'Possible risk of impaired fertility', R63 'Possible risk of harm to the unborn child' or R64 'May cause harm to breastfed babies'. Here it is assumed that the available mammalian toxicity data can give an indication on the possible risks of the chemical to higher organisms in the environment. If a substance is classified accordingly or if there are other indications, an assessment of secondary poisoning is performed.

At this stage a simple estimation is made if the PEC in water can lead to concentrations in fish that may lead to deleterious effects in higher organisms that eat fish. If secondary poisoning is to be avoided, the concentration of chemicals in the food should be below the No Observed Effect Level (NOEL) in dietary toxicity test with animals representative of fish-eating birds or mammals. The NOEL is considered as a maximum concentration in food which will not lead to adverse effects after ingestion of this food ($PNEC_{oral\ fish}$). When the bioconcentration factor (BCF) of a substance is known, the

PEC_{water} can be used to calculate the PEC in food (PEC_{oral}). This concentration can then be compared with $PNEC_{oral\ fish}$.

If no measured BCF is available, as is normally the case for new substances, an estimated BCF value based on the octanol/water partition coefficient is used. The decision to request a bioaccumulation test is based on the quantitative outcome of the assessment.

Secondary poisoning is only likely to be an issue for higher tonnage substances with wide dispersive use and which potentially can be taken up by biota. In practice, substances of concern will also tend to be persistent, exhibit negligible metabolism and have a log K_{ow} between 5-8. Dietary uptake by aquatic organisms is significant only if the compound has low water solubility, high lipid solubility, and is slowly metabolised or eliminated by the prey organism. When the BCF value is above 1000 - if predicted this would correspond to a log K_{ow} of 4.3 - a PEC/PNEC assessment for predators should be made, and refined as deemed necessary (ECETOC, 1995).

Biomagnification - defined as accumulation and transfer of chemicals via the food chain, resulting in an increase of the fat-adjusted internal concentration in organisms at succeeding levels in the trophic chain - is not as widespread as commonly believed. Biomagnification has only been demonstrated for a very limited number of substances (ECETOC, 1995).

Because the current EU-approach does not explicitly include the dietary pathway at lower tiers, it may underestimate the body burden of prey organisms for highly lipophilic compounds. It also initiates the assessment at a log K_{ow} of 3. The combination of these two factors suggests that the EU TGD would be overconcerned with compounds of little relevance for secondary poisoning, while underestimating actual exposure for compounds in the log K_{ow} range of 4.5 to 8 which are the most critical to dietary exposure.

Furthermore, it has been shown that the linear relationship between log K_{ow} and BCF is only true in a certain range. When the lipophilicity becomes high (log K_{ow} >6), the BCF starts to decrease due to lower bioavailability. Using a bilinear model (Bintein *et al*, 1993) derived from a large variety of chemicals, it can be calculated that log K_{ow} >8.5 lead to BCF <1,000, whereas linear models predict endless increase, which is not realistic. The parabolic model described in the TGD (Section 5.4.2.2), restricted to a certain class of chemicals is still overconservative. It is therefore suggested that the decision to request a bioaccumulation test be limited to $4.0 < \log K_{ow} < 8.5$.

The potential for bioaccumulation should only need to be evaluated if a substance is present and bioavailable in the water phase for a sufficiently long period and has a widely dispersive use pattern. According to the TGD, the parent molecule of chemicals with a hydrolysis half-life of less than 12

hours would be unlikely to bioconcentrate (EEC, 1993). Similarly, rapid biodegradation and/or photodegradation may significantly reduce the exposure concentration. However, there seems to be some confusion in the TGD as to whether to use PEC_{local} or $PEC_{regional}$ in the secondary poisoning calculations. The Task Force believes that $PEC_{regional}$ is more appropriate, whereas the TGD recommend a rather arbitrary average of the PEC_{local} and $PEC_{regional}$.

6. INDIRECT EXPOSURE

Indirect exposure is defined as exposure of the public via the environment, i.e. air, water, soil and food.

If indirect exposure is likely to occur, then it is necessary to estimate the relation between the concentration in each contact medium (air, water, soil) and transfer to food products and drinking water. In addition, it is necessary to assess dietary characteristics and food sourcing for the average individual or target group. Comprehensive indirect exposure assessments require measured concentration data for air, water, soil and food products, and measured data on ingestion (food, water, soil) and inhalation rates.

In the absence of measured data, predictions of concentrations in air, water and soil are needed to predict concentrations in drinking water and food products. Air, water and soil concentrations should be assessed regionally and average or typical diets should be assessed for the region (e.g. country) or target group (e.g. farmers, fishermen, babies) under consideration. The "regional assumption" is consistent with the observation that (1) people move around locally and in the region, and (2) food habits and sourcing will vary throughout the year. The average daily dose for each of these routes is the product of the average exposure concentrations in each contact medium (air, water, soil, food) with the average intake or uptake factor.

The total non-occupational exposure (consumer and indirect) or resulting total estimated intake for the average individual can then be used in the human health risk assessment and compared with intake criteria, such as acceptable and tolerable daily intakes. The relative contribution of indirect exposure as compared to consumer exposure will be largely overestimated if the human exposure via the environment is based on the unrealistic assumption that man is permanently living near or on the point source (i.e. PEC_{local}).

Before engaging in a discussion on how to predict or assess the concentration in a certain food type, it is necessary to evaluate or agree the food baskets of the average individual, or typical vegetarian, or any other target group (elderly vs. babies).

An estimate of the average consumption can be made from published statistical data (Euromonitor, 1992) and have been reported in ECETOC (1994c). It should be pointed out that more detailed diet studies have been performed within several EC member countries. Deviations from average food baskets (e.g. vegetarian diet) should be evaluated on a case-by-case basis. In addition, some learning from ECETOC (1994c) indicate that (1) potatoes need to be considered separately as they are a very important food source in Europe; (2) milk, yoghurt, butter and cheese should be considered

separately; (3) beef, veal and pork should be considered separately since in reality pork is the most important meat in all European countries; (4) fish is a relatively minor food source, except for Denmark, Portugal and Spain. Most fish will be from sea catches, rather than from inland waters.

The data show clearly that the typical food consumption is highly variable from country to country and in different regions of the same country and differences can be two- to three-fold, especially among vegetable foods (fruit, vegetables, cereals, potatoes). Use of the EC average figure gives a reasonable overall value, but other diets of target groups could be elaborated on the basis of the available data. This is merely an academic exercise since food sources may differ significantly according to species and region. In order to establish the food chain, it is therefore important to consider the origin of the feed. Many crops, including imported products, are used for animal feed production, rather than for food consumption. In the two models CSOIL or HESP (ECETOC, 1992) it has been assumed that only 10% of the food basket is sourced locally.

Quantitative structure activity relationships (QSARs) are needed to relate partition between water, soil and plants, and between animal diet, lipid tissue, and food produce. Insights in the limitations and uncertainties of these QSARs are currently limited. Although some data are available for a limited range of classical hydrophobic substances, extrapolation to other substances may not be appropriate. Validation and/or reformulation of these QSARs for a wider range of physico-chemical characteristics is needed if these "indirect QSARs" are to be used with confidence in the risk assessment process.

7. PREDICTION OF WORKPLACE EXPOSURES USING THE EASE MODEL

7.1 GENERAL ISSUES PRESENTED

EASE has been developed as a model for estimating workplace exposures for the purposes of 'new' and 'existing' substances risk assessment (EEC, 1996, Section 2.2.4). Like all models for estimating exposure, it must be used with circumspection and only *after* the suitability of other real or analogous data have been excluded.

EASE is an empirical model, based upon the considered experience of industrial hygienists within the UK Health and Safety Executive and making use of the extensive industrial hygiene data supporting their enforcement responsibilities. These data are historical and largely reflect exposure situations originating from activity in UK industry. The program is not able to take into account any exposure duration and may provide strong overestimations if only a few short-term exposure conditions (e.g. sampling) occur during daily work. The EASE model will always predict daily average (8 hour) exposure levels, although many exposure conditions as described in EASE will have a duration of no more than 15 minutes.

Despite its apparent simplicity, however, EASE is generally capable of estimating exposure to within one order of magnitude of those arising in practice *provided* the user has a sound knowledge of occupational hygiene. This sensitivity is such that EASE cannot be used as a 'benchmark' against which measured data could be compared: real or analogous data are preferred for risk assessment purposes. Moreover, in the context of those other areas of occupational health practice where airborne exposure data may be used e.g. targeting health surveillance programmes, the development of Occupational Exposure Limits, etc., EASE's utility remains unproved and its use must therefore remain restricted to within the scope of 'new' and 'existing' substance risk assessments.

7.2 SPECIFIC ISSUES

EASE acknowledges (EEC, 1996, Section 2.2.4.3.1) several shortcomings in its ability to address all aspects of workplace activity. However, some of these could be reduced or limited if the current guidance supporting EASE was clarified and improved. The functionality of the present version of EASE is similarly limited in a number of respects. In particular, EASE is currently unable to adequately assess exposures arising from:

- short term or acute exposures,

- exposure durations of less than 8 hours (unless the shift data are revised using simple adjustments),

- circumstances in the workplace which involve the use of personal protective equipment, and

- processes where the predominant aerosol generated is a mist.

The technical performance of EASE, together with user confidence in the product, should therefore be improved by:

- offering better clarity in the definitions of the terminology used to guide (both expert and non-expert) users through the model;

- incorporating further reference to other existing (and validated) models for the estimation of workplace exposures (see Appendix A);

- establishing a process which ensures the database against which EASE is validated remains current and representative of European workplace exposures;

- making available a help desk (contact telephone or e-mail, etc.) for immediate user enquiries; and

- commissioning a detailed (and transparent) evaluation of the software structure which is capable of subsequent support by other regulatory agencies.

7.3 IMPROVING THE CLARITY OF INDUSTRIAL HYGIENE TERMINOLOGY WITHIN EASE

The EASE program predominantly uses expert judgement to identify situations in the occupational environment which present a potential for significant exposure. EASE demands users possess an appropriate degree of industrial hygiene (or similar) knowledge and thus makes extensive use of industrial hygiene terminology in its structure. However, the underlying meaning behind each term used appears to reflect that in use within the UK.

In order that EASE is therefore more widely accessible to and understood by other EU partners, further guidance should be incorporated into either EASE (via Help Screens) and/or its supporting manual. Such an approach would offer better clarity on the definition of key terms and, through case

studies, provide examples of the context in which EASE uses such terms and their accompanying data.

In particular, further clarity should be given in the following key terms and areas:

1. *Local exhaust ventilation* (LEV) has a profound effect on the magnitude of workplace exposures to substances. This is reflected in EASE. However, whilst EASE incorporates the effect both 'good' and 'bad' LEV has on exposure, no clear guidance (EEC, 1996, Section 2.2.4.6) is given on what this constitutes.

2. In the case of exposures to dusts, EASE should address the role of *particle size* more fully. Apparent inconsistencies are present between the information contained in the Guidance to EASE (e.g. EEC, 1996, Section 2.2.4.6) and the logic indicated in the Decision Charts (e.g. EEC, 1996, Appendix I to Chapter 2, Fig.13). These anomalies do not devalue the usefulness of EASE. However, there is a need to distinguish between dusts which are liable to become airborne from those which are not. The role and definition of 'mobile solids' is not clear in this respect.

   A Help Screen should be provided to assist users to determine, at the outset, whether exposures to solids are relevant or not e.g. by clarifying the relevance of the 'mobile solid' option with regard to the inherent ability of a substance to become airborne. Issues such as inhalability and respirability are considered to be separate (but complementary) and capable to being addressed within the Guidance.

3. The definition of *'dry manipulation'* in the Decision Chart for non-fibrous solids (EEC, 1996, Appendix I to Chapter 2, Fig.14) requires clarification. In practice, a significant number of workplace activities might fall into this category. Currently, the guidance provided to assist users in its interpretation is limited.

   In order to improve the functionality of this key area of EASE (workplace exposures to non-fibrous dusts) the definition of 'dry manipulation' should be extended to include common fugacious activities which do not require the use of significant amounts of energy e.g. pouring, sifting, stirring, dis/charging. Similarly, the definition of *'readily aggregating'* particles should be expanded to include dedusted solids and those of a predominantly non-inhalable size range e.g. prills, flakes and beads.

4. EASE acknowledges (EEC, 1996, Section 2.2.4.4) that the sensitivity of the EPA approach used to estimate *dermal exposure* is limited (they are judgmental and hence could be described as "best guesses"). Whilst this aspect of EASE provides an output, its basis is unclear. The ability of the current EPA approach to assess dermal exposures to solids with a reasonable degree of accuracy

is doubtful. In some instances, it would appear to underestimate the importance of this route of exposure for substances having direct skin effects e.g. sensitisers, corrosives, etc.

If dermal exposure is considered to be important, then this aspect of EASE should be reviewed with the aim of improving it with respect to both:

- the quality of the guidance which supports unambiguous progress through the model, and
- the validity of the output (although it is acknowledged that little consensus exists on how this should be quantified).

If the logical basis for EASE is valid for airborne exposures, there is no reason why a similar logic process cannot be applied to the determinants of skin exposure, the pattern of use, the nature of controls and the characteristics of the substance (viscosity, dustiness, etc.). Partial validation of the outputs may be possible by reference to the data available from pesticide operator studies.

5. EASE is not able to take into account any exposure duration and may provide strong overestimations if only a few *short-term exposures* (e.g. sampling) occur during daily work. The role of other models in estimating exposures under limited and well defined conditions should be acknowledged. EASE would benefit by including further reference to other existing (and validated) models for the estimation of short-term exposure.

7.4 MAINTENANCE OF EASE

The usefulness of EASE is due, to a large part, to the fact that it is validated against actual exposure data. This feature is also a potential weakness, however. EASE is presently only validated against historical UK exposure data (EEC, 1996, Section 2.2.4.3.2). Moreover, it is unknown to what extent the data contained in the UK Health and Safety Executive National Exposure Database (NEDB) are representative of EU-wide exposures.

In order that EASE is able to provide sufficient confidence to users on the representativeness of its output to circumstances other than those in the UK, a mechanism for periodically recalibrating the model in a *transparent* manner should be established. Indeed, if such an exercise were to include data available from short term exposures, then this would possibly remedy a currently recognised weakness of EASE; there would not appear to be any substantive reason why the logic underpinning the ability of EASE to predict shift-long exposures could not also be applied to shorter time periods. In addition, industry should initiate further calibration of the EASE model by using industry exposure databases.

Consideration should therefore be given to introducing a formal review process for EASE which would ensure its output remains a true reflection of workplace practice across the EU and, via the involvement of relevant interested parties within the process, enable a wider ownership if EASE's benefits are to be realised.

8. CONSUMER EXPOSURE ASSESSMENT

8.1 INTRODUCTION

The assessment of consumer exposure is very well described in several recent publications including the EU TGD (EEC, 1996). While not legally binding, European competent authorities are encouraged to use the TGD to ensure harmonisation in the assessment of exposure to chemicals by the different Member States. Thus, the TGD is a practical tool for regulators when conducting an exposure assessment for both new and existing chemical substances.

The TGD describes an evaluation of the extent of the exposure of man through the use (both normal use and reasonably foreseeable misuse) of consumer products. Since the actual levels of chemical exposure (concentration in air, body/tissue dose etc.) are not usually measured during consumer product usage, mathematical models are provided in the TGD to allow estimates of the potential exposure to be generated. The models described are simple algorithms which may be suitable for certain product use scenarios both in the absence of actual use data and for comparison with exposure data available for the same or analogous products.

Over the last two years, regulators and industry scientists have had the opportunity to consider whether the TGD models are adequate for conducting assessments for consumers exposed to both new and existing chemicals. Both parties have also had the opportunity to recognise the limitations of these models in particular for higher tier assessments.

The principle areas of concern with the guidance provided on the estimation of consumer exposure in the EU TGD are:

- a lack of clear guidance for refining the exposure estimates where needed i.e. no guidance on the estimation of systemic uptake;
- the absence of guidance in the selection of various input parameters and justification of their use with the result that unrealistic exposure estimates may be obtained;
- the absence of a comprehensive database of human lifestyle factors including more extensive data on consumer habits and practices.

8.2 REFINING THE EXPOSURE ESTIMATE - SYSTEMIC UPTAKE

Comprehensive consumer exposure assessments require measured data to assess the extent of dermal, oral and inhalatory exposure of man to marketed consumer products and their components. Representative measured data on actual exposure and/or systemic absorption levels of a substance always take precedence over calculated data (EEC, 1996). Because it is often not possible or feasible to actually measure exposure under all circumstances of product use, it is justified to refer to standard exposure scenarios in such cases. The simple models described in the TGD text provide estimates only for the „external exposure" of the consumer i.e. the amount ingested, the total amount in contact with the skin or the amount of substance inhaled. Thus, the potential absorption of a substance into the body (systemic uptake) is not considered. In very many cases, this approach is sufficient since adequate margins of safety for the consumer are obtained when the hazard data are compared with these exaggerated exposure estimates.

Where the estimate of external exposure needs to be refined to calculate potential body uptake, a quantitative value may be quite easy to develop as in the case of accidental ingestion of a product or during the inhalation of a constant exposure level over a fixed period of time. In such cases, a value of 100% absorption as a default may be typically assumed.

The usefulness of the estimation of the exact absorption by inhalation or via ingestion is not clear. In general, the exposure level for inhalation (concentration in the air) and the dose for ingestion (mg/kg bodyweight) are directly related to the toxic effects observed in studies with test animals. The effects are normally not related to the amount retained and metabolised in the body. The route of absorption which is less frequently studied is the dermal route and therefore special attention is required in the estimation of the total dose absorbed dermally.

Dermal exposure is somewhat more difficult to quantify because of the known barrier properties of the skin. Contact with skin itself is not related to a default constant absorption rate for all chemicals. Therefore, dermal exposure deserves more extended discussion.

8.2.1 Uptake after Dermal Exposure

The data provided in the TGD concerning dermal exposure are mainly derived from actual usage measurements with cosmetics and detergent formulations. Using these practical examples for an exposure assessment for other consumer products implies that the physicochemical properties of a pure substances or those in a preparation hardly influence the potential for exposure. The TGD guidance assumes that dermal absorption is linearly related to skin exposure by means of the „fraction of uptake" factor. This is not supported by the scientific evidence on skin permeation. Skin

permeation is strongly influenced by the physicochemical properties of the substance and by the type and duration of skin contact i.e. the skin contact scenario. Clearly, where a refinement of the potential dermal exposure is required during risk assessment, then the TGD in its current form is not adequate since it does not address skin permeation or „uptake" sufficiently.

Alternative modelling packages such as CONSEXPO (van Veen, 1995) and SKINPERM (ten Berge, 1996) provide algorithms for a more reliable estimation of skin permeation. These modelling packages are referenced in the TGD.

The quantitative description of the skin permeation of chemicals is an area of physiology and toxicology in need of further research and development. It is, however, recognised that skin absorption is dependent on:

- the concentration of the chemical in direct contact with the skin;
- the duration of the skin exposure to the chemical;
- the physicochemical properties of the chemical which determine the rate of permeation through the *stratum corneum* and the epidermis.

Both chemical concentration and exposure duration are considered sufficiently in the TGD. However, the rate of permeation of a chemical through the skin layers is not discussed. Instead, it is assumed in the TGD that a thin film of constant thickness of the consumer product always covers a certain skin area. This assumed scenario is based on:

- contact of hands with the product in liquid form (e.g. in case of dish washing);
- contact of skin with deposited dust;
- leave-on cosmetics.

The extent of exposure is estimated from the total amount of product used and from the weight fraction of the chemical of interest. The total amount of exposure is then determined from the skin surface area covered by the product and the thickness of the thin film or product layer which is assumed to be on the skin (where the thickness of the film or product layer is not known, the TGD recommends the use of a default of 0.01cm).

The permeation rate through the skin layers may be determined experimentally. It is typically measured *in vitro* for human epidermis. A glass cell, separated into two compartments by the isolated

stratum corneum, is used. One compartment is filled with an aqueous solution of the chemical. The other compartment may contain physiological saline, which is continuously stirred.

Wilschut *et al* (1995) compiled numerous data on skin permeation. They developed a generalised approach for the estimation of the coefficient of permeation and also for the lag time for permeation based on two properties of the chemical: its octanol/water partition coefficient and its molecular weight. In addition, the water solubility of the chemical plays an important role in estimating skin permeation. In their model, the actual concentration of the substance in contact with skin does not exceed its water solubility. This starting point is essential, because:

- before the substance can be absorbed into the blood, it has to pass a thin aqueous layer which is unlikely to be passed by highly lipophilic chemicals;
- the skin permeation coefficient increases with increasing octanol/water partition coefficient;
- the actual permeation rate decreases with increasing octanol/water partition coefficient due to the decrease in water solubility.

Recently, Wilschut *et al* (1995) and Wilschut and ten Berge (1995) validated five skin permeation models for substances in aqueous solutions and studied the skin permeation of substances in the vapour phase. These models and their application in two different scenarios are discussed in Appendix B.

8.2.2 Uptake after Exposure via Inhalation

The TGD does not provide guidance on the selection of a model to estimate the potential absorption of chemicals after substance inhalation. The retention of inhaled volatile substances in the body is strongly dependent on:

- the duration of exposure to the volatile substance;
- the blood/air and the total body/air partition coefficients;
- the extent of metabolism of the substance once inside the body.

If exposure is very short, then the amount of substance absorbed is predominantly influenced by the blood/air partition coefficient of the substance. However, if the duration of exposure increases, then the extent of metabolism plays an increasingly important role. In Appendix C, the models presented in the CONSEXPO package (van Veen, 1995) on absorption after inhalation are discussed further.

8.2.3 Uptake after Exposure via Ingestion

The absorption by ingestion is normally not taken into account. Instead, for risk characterisation, the dose levels in animal experiments are directly compared with the estimated dose to which consumers may be exposed. The model in CONSEXPO predicts generally an uptake between 80 and 100 %. This may not be always true in case of highly lipophilic substances. In such cases, the water solubility is the absorption rate limiting factor and these substances are unlikely to be absorbed but excreted via the faeces. The solubility of the compound is not accounted for in the estimation of absorption by ingestion.

8.3 SELECTION OF MODEL INPUT PARAMETERS

The TGD describes some simple algorithms for estimating potential exposure of consumers to chemical substances during the use of consumer products and these algorithms contain parameters for which input is needed. Values for various parameters needed in a model are provided in the document's appendices but these represent data only for certain types of consumer products (household cleaning products, cosmetics, textiles containing dyes) and guidance for other types of products is not available. Where worst case scenarios are to be considered, the document recommends using the upper estimates of ranges provided for the amount of product used per event, the frequency of the event (and therefore the frequency of exposure) and the typical duration of the event. The document also cautions the user not to grossly exaggerate the final exposure estimate by using only maximum values for parameters in the calculation, particularly if these values are correlated with each other. In the absence of actual data, the user is also recommended to use default values for certain parameters.

However, this guidance is only of a very general nature. The document would benefit from some examples of how to handle various input parameters; how to determine whether the available data are representative and whether their use would be appropriate; how to determine whether the recommended default is meaningful and relevant for the case in hand and how to determine whether some values are dependent on each other. More guidance would also be useful on how to do a „reality check" on the exposure estimate in order to understand whether the estimate is indeed realistic. A sensitivity analysis would be useful. If alternate models are used such as those described in the appendices of the TGD [CONSEXPO, THERDBASE (Pandian *et al*, 1990), SKINPERM] for estimating actual absorption, no guidance is provided on how to select the more complex models needed e.g. for addressing possible dermal absorption (uptake fraction, diffusion etc.).

Overall, the TGD needs some clear examples or case studies to help particularly the inexperienced user with the use of exposure models and the selection of input parameters.

8.4 COMPREHENSIVE DATABASE FOR HUMAN LIFESTYLE FACTORS

The TGD contains several references to available literature on standard scenarios for use of consumer products (e.g. US-EPA, 1989) and includes some useful tables of data needed for model input (e.g. mean body surface areas). However, while some of these data are generic, others are clearly specific to a particular geography or region and therefore may not be useful or appropriate for some exposure calculations. More data need to be provided to help address specific habits and practices of user groups. Further, more data on various human lifestyles are needed in the form of „time budget data" i.e. information on the specific activities of a population over time (during a day, a year etc.). The question of how to evaluate these data in terms of their statistical significance is also not considered.

The need for a more comprehensive database is highlighted in the TGD text, but there is insufficient guidance given on how to obtain such data and how to evaluate their possible usefulness for an exposure assessment.

9. RECOMMENDATIONS

Release Estimates

It is proposed that future work on release estimates should focus on improving the use category documents. This potentially requires a great deal of work and access to what may often be considered to be company-sensitive information. It is thus envisaged that any such activity will involve collaborative work between different companies and industries. A mechanism is needed in order to facilitate such collaboration, possibly via industry sector groups or trade associations.

Calculation of $PEC_{regional}$

In the case of point sources, fate processes and contributions from other sources will become increasingly important. Therefore, the deterministic calculation of $PEC_{regional}$ may involve considerable effort and values determined may vary considerably. Therefore, a stochastic approach should be taken into account in order to estimate the $PEC_{regional}$.

Biodegradation in surface water, sediment and soil

The Task Force believes that the tables provided in the TGDs are probably extremely conservative. There is a general lack of kinetic biodegradation data which could form the basis for extrapolation of screening test results from laboratory to the real environment. Data generation in this field is considered to be important for a more realistic risk assessment and it is recommended to develop an empirical database. Biodegradation in the adsorbed stage (particularly important for substances with high Koc) both under aerobic and anaerobic conditions should be considered with priority, taking into account bioavailability.

Bioaccumulation

The potential for bioaccumulation needs only to be evaluated if substances are of widely dispersive use and are present and bioavailable in the water phase for a sufficiently long period of time. There seems to be some confusion in the TGD over whether to use PEC_{local} or $PEC_{regional}$ in the secondary poisoning calculations. The Task Force believes that $PEC_{regional}$ is more appropriate, whereas the TGD recommend a rather arbitrary average of the PEC_{local} and $PEC_{regional}$.

Prediction of workplace exposures using the EASE model

Consideration should be given to introducing a formal review process for EASE which would ensure its output remains a true reflection of workplace practice across the EU and, via the involvement of relevant interested parties within the process, enable a wider ownership if EASE's benefits are to be realised.

Model development

Assessments should move from 'risk characterisation' by means of PEC/PNEC comparisons to 'risk estimation', i.e. the quantification of the likelihood of the incidence and severity of adverse effects, characterised in terms of a statistical distribution with a most probable value for the risk and some confidence interval and not by a single number. ECETOC has started a project entitled 'ECIMOS' with the objective of developing an Integrated Modelling System or common modelling platform for exposure, effect and risk modelling using existing model algorithms or calculation modules which integrate state-of-the-art methods for sensitivity and uncertainty analysis for different aspects in the exposure, effect and risk assessment of chemical substances.

APPENDIX A. PREDICTIVE MODELS FOR ESTIMATION OF EXPOSURE IN THE WORKPLACE

A.1 BACKGROUND

In case of prediction of exposure in the workplace the following types of models can be used (Buringh and Lanting 1991):

- *empirical models.* Examples are the distribution probability model (log-normal statistics), the model based on a Markov process (estimating means and confidence limits over periods T > observation period) or autoregressive (integrated) moving average models. The EASE model is an empirical model;

- *deterministic models* like single point source (concentration dependent on source, turbulent diffusion, distance and ventilation rate) and single box model (concentration dependent on source and ventilation rate);

- *hybrid models* like the autoregressive moving average model including an explanatory variable X related to the emission source or like regression models weighing the influence of workplace variables and emission source strength.

A.2 SHORT TERM EXPOSURE MODELS

Matthiesen (1986) developed some reasonable worst case estimations for short term inhalation exposure of liquids with a certain vapour pressure. He was responsible for the occupational exposure and environmental release assessment of existing chemicals under the Toxic Substances Control Act. He considered three main scenarios:

Maintenance scenario

A worker is repairing a reactor vessel with an open manway. It is assumed that vapour is released by evaporation of a liquid layer in the reactor vessel. The vapour released is diluted by ventilation. The concentration inhaled is estimated by equation A.1:

$$C = \frac{4.8 * P_o * A * (18/M)^{0.33}}{k * Q} \qquad \text{(Equ. A.1)}$$

C = predicted concentration in ppm
P_o = saturated vapour pressure in Pa
A = manway opening area (0.65 m^2)
M = molecular weight
k = mixing factor (0.1 to 0.5)
Q = ventilation rate (85 m^3/minute)

Sampling scenario

A worker fills a bottle from a sample tap. It is assumed that volatilisation of the liquid is the driving force and not the displacement of vapours from the sample container, because sample containers are usually small. Therefore Equation A.1 is used, in which only A is revised:

A = sample bottle opening (0.004 - 0.008 m^2)

Filling containers with liquid

Vapour is released by displacement of the vapour in the container during filling and by volatilisation. The volatilisation of the liquid surface is assumed to be negligible compared to the displacement of vapour. Therefore only the displacement of vapour is considered. The resulting worker concentration from filling of drums, trucks or tank cars is controlled by:

- the volume and number of vessels filled per hour;
- the way of filling (splash loading or subsurface loading).

The following equation predicts more or less the concentration of the vapour during loading:

$$C = \frac{10 * f * V * r * P_o}{k * Q} \qquad \text{(Equ. A.2)}$$

C = predicted concentration (ppm)
f = splash loading f=1, subsurface loading f=0.5
V = volume of vessel (m^3)
r = filling rate, number of vessels/hour (e.g. 20-30 for vessels of 0.2 m^3, 2 for vessels of 5 m^3 and 1 for vessels of 20 m^3)
P_o = saturated vapour pressure at loading temperature (Pa)

k = mixing efficiency of ambient air (0.1-0.5)

Q = ventilation rate (5,100 m^3/hour in outside air)

A.3 LONG TERM EXPOSURE SCENARIOS (Roach, 1992)

The long term exposure models may be subdivided into a single point source and a single box model.

Single point source model (Roach, 1992, Wadden *et al,* 1991)

In this model it is assumed that supply of fresh air and discharge of contaminated air occurs through openings distributed around the periphery. An analogous model of ventilation showing symmetry about a source would be a hollow hemisphere. The radius R of this hemisphere is more or less arbitrarily estimated. For a room with a length L, a width W and a height H, R is approximated by:

$$R = \frac{L + W + H}{W/2} \qquad \text{(Equ. A.3)}$$

According to the basic assumptions of the model the source is located more or less in the middle of the room.

The concentration at a certain distance from the source is now approximated by:

$$C = \frac{E}{Q} + \frac{E}{2\pi D}\left(\frac{1}{r} - \frac{1}{R}\right) \qquad \text{(Equ. A.4)}$$

C = concentration of contaminant in air (mg/m^3)

E = source strength (mg/sec)

Q = volume flow rate out of room (m^3/sec)

D = diffusivity (approximately 0.05 m^2/sec)

R = radius of hemisphere (m)

r = distance from source (m).

There are estimates of the natural ventilation without mechanical exhaust equipment. This lies between 5×10^{-4} and 5×10^{-5} m^3/sec/m^2 wall surface. The wall surface is 2H x (L + W) = A m^2. The natural ventilation of the room varies from 5×10^{-4} x A to 5×10^{-5} x A. In this way guidance is provided whether or not mechanical ventilation is needed to reduce exposure levels.

Single box model

It is assumed that contaminant release occurs at many places in a room, that the contaminant is homogeneously mixed and removed from the room by ventilation with outside air. The concentration can easily be estimated by:

$$C = \frac{E}{Q} \qquad \text{(Equ. A.5)}$$

E = source strength (mg/sec)
Q = volume flow rate out of room (m^3/sec)

A.4 ESTIMATION OF SOURCE STRENGTH

The estimation of the source strength is key factor in the models above. The source strength may be derived from:

- the necessary supplementary volume per week or per month of solvent for cleaning purposes;
- estimation of the evaporation rate of solvents from the surface layer dependent on the velocity of air in contact with the liquid layer. Turbulent and unpredictable air velocities of 0.1 to 0.25 m/sec are quite common.

$$E = 2000 * Vl^{0.78} * Rp^{-0.11} * \frac{Mw * 101325}{8314 * (Tc + 273.15)} * \ln\left(1 + \frac{Pa}{101325 - Pa}\right) \qquad \text{(Equ. A.6)}$$

E = evaporation rate (mg/m^2/sec)
Vl = air velocity (m/sec)
Rp = radius of liquid pool (m)
Mw = molecular weight
Tc = ambient temperature in °C
Pa = saturated vapour pressure (Pa)

Although this equation is applied for liquid spills in open industrial areas, it may be used as a first approximation of the evaporation of volatile liquids.

APPENDIX B. MODELS FOR SKIN PERMEATION

B.1 SKIN PERMEATION FROM AQUEOUS SOLUTIONS

By means of an extensive data set of experimentally measured skin permeation coefficients (K_p), Wilschut *et al* (1995) developed a model which allowed the prediction of K_p which were in close agreement with the experimentally measured values. In this model, the skin structure is considered to consist of:

- the *stratum corneum* layer with separate permeation coefficients for a polar protein layer, K_{pol}, and for a lipid layer, K_{lip};
- an aqueous layer situated below the *stratum corneum* with its own permeation coefficient, K_{aq}.

The permeation coefficients are combined to give one overall K_p according to the following equations:

Overall permeation coefficient:

$$K_p = \frac{1}{\frac{1}{K_{lip} + K_{pol}} + \frac{1}{K_{aq}}} \qquad \text{(Equ. B.1)}$$

Permeation coefficient of lipid fraction of *stratum corneum*:

$$K_{lip} = 10^{(-1.326+0.6097 \cdot \log K_{ow} - 0.1786 \cdot Mw^{0.5})} \qquad \text{(Equ. B.2)}$$

Permeation coefficient of protein fraction of *stratum corneum*:

$$K_{pol} = \frac{0.0001519}{\sqrt{Mw}} (cm/h) \qquad \text{(Equ. B.3)}$$

Permeation coefficient of the aqueous layer:

$$K_{aq} = \frac{2.5}{\sqrt{Mw}} (cm/h) \qquad \text{(Equ. B.4)}$$

The above equations are recommended for estimation of the skin permeation from aqueous

$$M = K_p \cdot T \cdot O \cdot C \qquad \text{(Equ. B.5)}$$

solutions. In order to estimate the skin permeation (M) the following equation may be used:

M = skin permeation (mg)
T = exposure time (h)
O = surface exposed (cm^2)
C = concentration of substance (mg/cm^3)

Equation B.5 may be also used as a first conservative approach for short exposure periods; the concentration C may never exceed the water solubility.

B.2 SKIN PERMEATION BY VAPOURS

Recently, Wilschut and ten Berge (1995) studied the skin permeation of vapours on the basis of published experimental observations. In the case of substances with a molecular weight < 200 and a vapour pressure > 15 Pa, the following empirical equation could be derived by multiple linear regression analysis:

$$K_{pa} = 3.277 - 0.3754 \cdot \log K_{ow} - 0.7666 \cdot \log V_p \qquad \text{(Equ. B.6)}$$

K_{pa} = permeation coefficient of the skin from air (cm/h)
K_{ow} = octanol/water partition coefficient
V_p = vapour pressure (Pa)

The absorption by the skin is estimated as follows:

$$M_v = K_{pa} \cdot C \cdot T \cdot O \qquad \text{(Equ. B.7)}$$

M_v = mass of substance permeated through the skin (mg)
C = concentration of substance (mg/cm^3)
T = exposure time (h)
O = surface exposed (cm^2)

Unfortunately, the permeation of vapour through the skin was studied only for 14 substances. Therefore, an alternative way for estimating the skin permeation by vapours was developed.

The permeation coefficient of a substance from aqueous solutions was converted into a permeation coefficient from air, K_{psk}, by multiplication with the water/air partitioning coefficient, K_{wa}. In addition, the extent of diffusion of the substance in air, D_{air}, and the diffusive path, δ, were defined in order to estimate the mass transfer coefficient from air to skin, K_{pair}. The permeation coefficients, K_{psk}, and the mass transfer coefficient, K_{pair}, were combined to give the K_{pa}.

$$K_{psk} = K_p \cdot K_{wa} \qquad \text{(Equ. B.8)}$$

where $K_{wa} = \frac{8.314 \cdot 298 \cdot Wsb}{Vp \cdot Mw}$

$$D_{air} = 360 \cdot \sqrt{\frac{76}{Mw}} \; ; \quad K_{pair} = \frac{D_{air}}{\delta} \qquad \text{(Equ. B.9; B.10)}$$

$$K_{pa} = \frac{1}{\frac{1}{K_{psk}} + \frac{1}{K_{pair}}} \qquad \text{(Equ. B.11)}$$

Wsb	=	water solubility (mg/l)
Vp	=	vapour pressure (Pa)
Mw	=	molecular weight
K_{wa}	=	water/air partitioning coefficient
K_p	=	permeation coefficient skin from water (cm/h)
K_{psk}	=	permeation coefficient skin from air (cm/h)
D_{air}	=	diffusivity in air (cm^2/h)
δ	=	layer of stagnant air, assumed for light clothes (assume 3 cm)
K_{pair}	=	mass transfer coefficient from air to skin (cm/h)
K_{pa}	=	overall permeation coefficient from air (cm/h)

B.3 SCENARIOS FOR SKIN PERMEATION

The guidance document does not make a clear distinction between scenarios for skin contact events. It is important to distinguish between scenarios in which the concentration of the substance in the preparation is constant during the contact time and those in which a certain amount of product is applied upon the skin without removal.

Scenarios in which the concentration of the substance in the preparation is constant during the contact time

The following situations are typical for such scenarios:

- skin in contact with aqueous solutions for washing dishes or clothes;
- cleaning activities with solvent mixtures by means of a polishing cloth;
- transfer of substances from clothes to skin taking into account the amount of sweat produced per hour (40 ml per hour for an adult; ICRP, 1974); the average surface of wet skin in contact with clothes is assumed to be 1,000 cm^2.

In these scenarios skin permeation in mg (M) can be simply estimated by means of equation B.5. The overall permeation coefficient, Kp, is measured or estimated by means of the equations presented in Appendix B.1.

Equation B.5 is recommended for estimation of the skin permeation from all types of liquid matrices in contact with skin for a certain period, in which the concentration in the matrix does not change. For all types of matrices, it is assumed that partitioning occurs between matrix and water, that the water layer is in real contact with the skin and that the level of the substance in the water layer will never exceed the water solubility.

Scenarios in which a certain amount of product is applied upon the skin without removal

The following situations are typical for such scenarios:

- leave-on cosmetics;
- incidental contacts with paints or viscous solutions.

It is assumed that the layer in contact with skin is so thin that it is well mixed and not stratified. Furthermore, it is assumed that immediate partitioning occurs between the substance and the *stratum corneum* (worst case assumption). The extent of skin permeation is strongly influenced by the physico-chemical properties of the substance. Volatile substances will evaporate faster than being absorbed via the skin into the body.

In the case of absorption via the *stratum corneum,* the substance has to pass the *stratum corneum* and the aqueous layer just below the *stratum corneum.* The absorption is assumed to be related to the combined permeation coefficients of the *stratum corneum* and the aqueous layer.

For evaporation, the compound has to pass the *stratum corneum* and a thin layer of air just above the skin. The evaporation is assumed to be related to the combined permeation coefficients of the *stratum corneum* and the air layer above the skin.

The fraction being absorbed, F_{ab}, may be derived from:

$$F_{ab} = \frac{K_p}{K_p + K_{ev}} \qquad \text{(Equ. B.12)}$$

The estimation of K_p is provided in Section B.1. The evaporation rate, K_{ev}, is mainly influenced by the vapour pressure of the substance in the preparation, the diffusion coefficient in air and the layer of air above the skin to be passed by diffusion. The estimation of K_{ev} is provided below.

The estimation of K_{ev} is as follows:

$$K_{aw} = \frac{Vp * Mw}{R * T * Wsb} \qquad \text{(Equ. B.13)}$$

$$K_{ev} = \frac{1}{\frac{1}{K_{psc}} + \frac{1}{K_{pair} * K_{aw}}} \qquad \text{(Equ. B.14)}$$

Wsb	=	water solubility (mg/l)
Vp	=	vapour pressure (Pa)
Mw	=	molecular weight
K_{aw}	=	air/water partitioning coefficient

R	=	gas constant (8.314 [Pa x ^{m3}]/[Mol x °K]
T	=	temperature (°K)
K_{psc}	=	permeation coefficient *stratum corneum* (cm/h)
D_{air}	=	diffusivity in air (cm^2/h) (Equ. B.9)
d	=	layer of stagnant air (best estimate 1 cm for unprotected skin)
K_{pair}	=	mass transfer coefficient from skin to air (cm/h) (Equ. B.10)
K_{ev}	=	overall permeation coefficient from *stratum corneum* to air (cm/h)

This approach will guarantee that the impact of physico-chemical properties of the substance on skin absorption is correctly taken into account. In Table B.1 the fraction absorbed was estimated by means of the equation above.

Table B.1. Fractions of Substances Absorbed via the Skin (calculated from Equation B.12)

Substance	Fraction Absorbed via Skin
Aroclor 1242	1.07×10^{-1}
naphthalene	9.27×10^{-1}
benzene	3.55×10^{-1}
toluene	2.34×10^{-1}
xylene	2.29×10^{-1}
styrene	5.17×10^{-1}
ethyl benzene	2.13×10^{-1}
n-hexane	4.59×10^{-4}

APPENDIX C. MODELS FOR ABSORPTION AFTER INHALATION

In the program CONSEXPO (van Veen, 1995) the retention of inhaled volatile substances is estimated for the first few inhalations after the start of exposure. In this case, the amount taken up is only dependent of the blood/air partition coefficient. It is simply a partitioning of the substance between the inhaled air and the blood volume in the lungs. This model is valid for a period of up to 10 minutes.

If exposure takes place over a longer period, the duration of exposure and the metabolism are increasingly more important. This is explained in the model below:

The uptake rate U is defined by:

$$U = A_l \cdot P_l \cdot (C_a - K_{ab} \cdot C_b) \qquad \text{(Equ. C.1)}$$

A_l	=	area of lung wall (m^2)
P_l	=	permeability of the lung wall (m/h)
C_a	=	substance concentration in lung air (mg/m^3)
K_{ab}	=	air/blood partition coefficient
C_b	=	substance concentration in blood (mg/m^3)

The term A_l x P_l has the dimension of m^3/h and is identical with a parameter like alveolar ventilation. The uptake rate is not assumed to be influenced by any metabolism in the body.

If the uptake from the blood compartment is considered and assuming that (only for modelling purposes) the tissue level will be more or less equal to the blood level, then the following equations can be derived:

$$\frac{dC_b}{dt} = \frac{V}{W} \cdot (C_a - \frac{C_b}{R_{ba}}) - k \cdot C_b \qquad \text{(Equ. C.2)}$$

$$\frac{dC_b}{dt} = V \cdot \frac{C_a}{W} - \left(\frac{V}{R_{ba} \cdot W} + k \right) \cdot C_b \qquad \text{(Equ. C.3)}$$

$$C_b(t) = \frac{\frac{V \cdot C_a}{W}}{\frac{V}{R_{ba} \cdot W} + k} \cdot \left(1 - e^{-\left(\frac{V}{R_{ba} \cdot W} + k\right) \cdot t}\right) \qquad \text{(Equ. C.4)}$$

The concentration in blood at equilibrium, C_{beq}, may now be formulated as follows:

$$C_{beq} = \frac{V \cdot R_{ba} \cdot C_a}{V + k \cdot R_{ba} \cdot W} \qquad \text{(Equ. C.5)}$$

V	=	alveolar ventilation (l/min)
C_a	=	concentration in alveolar air (mg/l)
C_b	=	concentration in blood (mg/l)
W	=	body volume (l)
k	=	metabolic rate (min^{-1})
R_{ba}	=	blood/air partitioning coefficient

If the term k x R_{ba} x W is much greater than V, then the level in the blood is linearly related to the volume V inhaled per time unit and the amount of substance metabolised. If k x R_{ba} x W is much less than V, then the alveolar ventilation will hardly affect the equilibrium concentration in the blood and the amount of substance metabolised. In order to estimate the uptake of a chemical, the rate of metabolism needs to be known. The inhalatory diffusion model of CONSEXPO is valid for short exposure periods, but for periods longer than one hour, the metabolic rate should be taken into account.

Furthermore, C_a should be discussed in more detail. The above presentation of the model is only a rough approximation and it is assumed that the level of the substance in alveolar air is more or less identical to the level in inhaled air. In practice the equilibrium level in alveolar air is lower than in inhaled air due to uptake by the blood.

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