DEUTSCHER BUNDESTAG

Ausschuss für Umwelt, Naturschutz und Reaktorsicherheit
15. WP

Ausschussdrucksache 15(15)320*

Öffentliche Anhörung „REACH“
Ratsdok.-Nr. 15409/03

am 8. November 2004 in Berlin

vom Bundesinstitut für Risikobewertung zur Verfügung gestellte Materialien

- REGULATORY TOXICOLOGY. Animal testing and alternative approaches for the human health risk assessment under the proposed new European chemicals regulation

- Presseveröffentlichung des BfR 18/2003: „Geplantes Europäisches Chemikaliensystem bringt Fortschritte für den gesundheitlichen Verbraucherschutz“

- Das Konzept „Verwendungs- und Expositionskategorien“ - Standpunkt der deutschen Bewertungsbehörden. September 2004 Bundesanstalt für Arbeitsschutz und Arbeitsmedizin / Umweltbundesamt / Bundesinstitut für Risikobewertung

Arch Toxicol (2004) 78: 549–564
DOI 10.1007/s00204-004-0577-9

REGULATORY TOXICOLOGY

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Animal testing and alternative approaches for the human health risk assessment under the proposed new European chemicals regulation

Received: 10 January 2004 / Accepted: 8 April 2004 / Published online: 29 May 2004

Abstract During the past 20 years the EU legislation for the notification of chemicals has focussed on new chemicals and at the same time failed to cover the evaluation of existing chemicals in Europe. Therefore, in a new EU chemicals policy (REACH, Registration, Evaluation and Authorisation of Chemicals) the European Commission proposes to evaluate 30,000 chemicals within a period of 15 years. We are providing estimates of the testing requirements based on our personal experiences during the past 20 years. A realistic scenario based on an in-depth discussion of potential toxicological developments and an optimised "tailor-made" testing strategy shows that to meet the goals of the REACH policy, animal numbers may be significantly reduced below 10 million if industry would use in-house data from toxicity testing, which are confidential, if non-animal tests would be used, and if information from quantitative structure activity relationships (QSARs) would be applied in substance-tailored testing schemes. The procedures for evaluating the reproductive toxicity of chemicals have the strongest impact on the total number of animals bred for testing under REACH. We are assuming both an active collaboration with our colleagues in industry and substantial funding of the development and validation of advanced non-animal methods by the EU Commission, specifically in reproductive and developmental toxicity.

Keywords Animal experiments · EU chemicals policy · Hazard assessment · Regulatory toxicology · Risk assessment

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Introduction

In 2001, the European Commission published a policy statement on future chemicals regulation and risk reduction entitled "White Paper: Strategy for a Future Chemicals Policy" (EU COM 2001). Recently, after the EU Commission developed specific regulations and presented them for a web-based discussion (EU COM 2003a, b), the amended proposal for a new directive was submitted to the EU Parliament and the European Council (EU COM 2003d). The development of the new chemicals policy has been driven by the unsuccessful current approach for risk management of the majority of existing chemicals. Driven by the aim to finalise the risk assessments for all existing chemicals within 12–15 years, the need for obtaining data on the hazardous properties of these chemicals became urgent. During the last two decades of the current legislation, industry did not comprehensively test their chemical products, partly because of a lack of incentives for hazard identification based on appropriate toxicological testing. The hazard and risk assessment of all existing chemicals not tested in the past will inevitably need "retrospective" toxicological testing. ECOPA, the European Consensus Platform on Alternatives, a non-governmental initiative by scientists, had raised concerns that substantial increase in laboratory animal testing may result from the proposed regulation (see http://ecopa.vub.ac.be). The actual legal proposal (EU COM 2003d) is based on several adjustments of the original concept (EU COM 2003a, b). It includes specific details of the recently proposed REACH-system:

- The *registration* of all chemicals
- The *evaluation* procedures within industry and the development of tailored testing
- The regulation of the *authorisation* of high-risk substances (in particular carcinogenic, mutagenic and reprotoxic chemicals)
- The establishment of a new European agency for the regulation of *chemicals* and several stakeholder committees

To put the discussion on the need for mammalian testing under the REACH program on solid ground, we are providing an estimate of the testing requirements based on our personal experiences during the past 20 years in the national regulatory agency in Germany that is responsible for the risk assessment of chemicals. In discussing the need for experimental animals we do not restrict ourselves to the definition of experimental animal as laid down by EU regulations (see: EU 1986, 1998). We include all animals that will have to be bred to live under experimental conditions to allow for any toxicological evaluation based on the REACH regulation either as exposed animals or as controls. Although this report is written from a European perspective, it is also relevant for regulatory toxicologists outside Europe, since all chemicals that enter the European Union will have to be assessed by regulatory standards of the EU.

Test methods for identifying health hazards

Testing methods

Over several decades in vivo tests have been developed and refined with the aim to detect and characterise inherent toxic properties and their dose-effect relationships. The tests have been standardised at an international level within the OECD Test Guideline Programme. Although acceptance is mandatory for OECD member countries only, their results are accepted by regulators throughout the world. The tests cover the most important health endpoints for safe handling of chemicals and products, including transport and use.

Although the White paper (EU COM 2001) as well as the European Parliament (EU Parliament 2001) suggest that in the first place testing should be restricted to in vitro tests, a general agreement on appropriately validated in vitro tests is still missing. In co-operation with external partners, including some of the authors, the European Centre for the Validation of Alternative Methods ECVAM has recently put forward a comprehensive overview on the status of toxicological non-animal methods (Worth and Balls 2002). In 2001 and 2002 the MRC Institute for Environment and Health of the University of Lester (UK) published, on behalf of the UK government, several reports on the feasibility of replacing animal tests with in vitro methods under the new EU chemicals policy approach (IEH 2001a, b, 2002). The perspectives for applying in vitro safety tests have to be evaluated carefully, taking into account both the toxicological endpoints and hazards to be assessed. We will therefore discuss these perspectives and challenges, focussing on the most important endpoints of toxicity in the individual chapters of this report.

Structure-activity relationships: (Q)SAR

The most simple approach to use structure-activity relationship (Q)SAR considerations for regulatory evaluation is the informal approach of using personal toxicological judgement on comparable chemicals. This is in fact the established procedure for 10–20% of all notifications of new chemicals within competent authorities in the European Union and in the respective US agencies (Hanway and Evans 2000; Cronin et al. 2003). A prerequisite condition for this ''read-across approach'' is the similarity of chemicals with respect to their molecular structure and physicochemical data.

In 2000, the OECD started to collect information on (Q)SAR models for the prediction of toxic effects of chemicals currently on the market. The models in most widespread use for toxicology are Multi-CASE (Klopman 1985; Klopman and Rosenkranz 1994), TOPKAT (Enslein et al. 1994) and DEREK (Sanderson and Earnshaw 1991). (Q)SAR models have successfully been used for many years by institutions of the federal US government (EPA, FDA, NCI), by the US National Toxicology Program (NTP) and also by European authorities in Denmark, the United Kingdom, The Netherlands and Germany. Experts at the Danish Environmental Protection Agency have used computer modelling based on Multi-CASE and TOPKAT in order to predict acute oral toxicity, sensitisation, mutagenicity, and carcinogenicity for up to 22,000 chemicals (Danish EPA 2001). Multi-stakeholder evaluation initiatives were active in:

- Collection, evaluation and verification of published (Q)SAR rules in order to support the development of new systems (Hulzebos et al. 2003)
- Discussing the above mentioned (Q)SAR systems for the purposes of REACH (Hulzebos and Posthumus 2003; Rosenkranz 2003)
- Amendment of existing (Q)SAR prediction systems such as DEREK based on regulatory experience in the assessment of new chemicals in the EU (Gerner et al. 2003)

Recently, two critical reviews on (Q)SAR models for assessing human health risks of chemicals have been published (Walker et al. 2002; Eriksson et al. 2003). (Q)SAR models have not been evaluated for general use in toxicology; however, in a recent OECD workshop, the potential of those models for chemicals management was emphasised (Jaworska et al. 2003) and the problems that must be solved prior to their use as toxicological assessment tools were identified (Walker et al. 2003).

Promising results in some areas of application are confronted with disappointing predictions in the field of carcinogenicity. It must be emphasised that (Q)SARs are effective in simulating specific toxic effects and reactions such as irritation, sensitisation or mutagenicity (Cronin et al. 2003). However, general multi-stage toxicological processes are difficult to simulate (Rosenkranz 2003). When drafting REACH, the EU Commission carefully noted the limitations of (Q)SAR: *''Results obtained from suitable SAR-models may predict...a certain dangerous property.''* This indicates that the use of (Q)SAR models

is intended for pre-evaluation in particular. ECETOC has recently published an evaluation of the current status of publicly available (Q)SAR model software with respect to current hazard prediction power and current practical applicability for users without specific (Q)SAR experience (ECETOC 2003).

Human experience

Whereas testing on humans solely for hazard identification purposes is generally not acceptable (see Globally Harmonised System of Classification and Labelling of Chemicals, United Nations 2003, para. 1.3.2.4.7), epidemiological data and experiences from exposure of humans to chemicals may provide a basis for evaluating human health hazards. The assumption (e.g. stated by Combes et al. 2003) that the hazardous potential of many of the existing chemicals should already have been detected from adverse effects in humans, however, is unrealistic due to the lack of appropriate epidemiological studies to detect an increase in effect over background level, e.g. cancer incidence, which is only moderate from the statistical point of view but meaningful from the perspective of public health. It has to be taken into account that the negative result of an epidemiological study does not prove the absence of an intrinsic hazardous property of a substance. However, it is feasible to estimate post-hoc the threshold level of a toxic effect which at a given level of statistical confidence would not have been detected in the study. This information is important for an overall assessment of the magnitude of a specific risk to humans. In some instances, e.g. cancer risk or the risk of malformations, results from properly conducted epidemiological studies provided both the ultimate proof of an existing risk for humans and in addition an estimate of its magnitude.

There are no regulatory guidelines today on how to use human experience data for classification into specific hazard categories. In case of poisoning or target organ toxicity, human experience will often need auxiliary animal testing data for classification. Under EU regulations, classification for mutagenicity, carcinogenicity, reproductive toxicity, aspiration and respiratory sensitisation can already be derived from human experience. However, in the future, the situation will be different when the GHS, the Globally Harmonized System for Classification and Labelling (United Nations 2003), is implemented. One of the new topics of the International Programme of Chemical Safety (IPCS) aims at using data from poison control centres in the risk assessment process. It has become obvious that this approach is less capable of identifying chronic effects (WHO/IPCS 2002a). Acute and subacute effects may be identified only after improvement of existing standards for registration and documentation (WHO/IPCS 2002b). In addition, the criteria for classification and labelling based on human experience should be defined more stringently.

Reducing the volume of testing

The main approach to refrain from additional animal experiments is to provide access to results derived in the past in testing laboratories and make them available by including them in existing databases. A definite regulation for mandatory publication of all existing animal testing results in the European Union or even in all OECD member states would be highly appreciated to avoid any duplication of testing at a worldwide level.

The highest proportion of existing toxicological data, published or kept confidential, has been generated according to protocols that are different from current OECD Test Guidelines (TGs) and the studies may not have been conducted according to Good Laboratory Practice (GLP) standards. However, since these studies may provide important information despite technical deficits, acceptance criteria have been developed to evaluate the existing information (Klimisch 1997). We discourage the common practice used by industry to undermine the results of such old studies whenever they show signs of severe toxicity. There is no scientific reason to conduct new GLP studies according to OECD Test Guidelines to show less severe results and, hence, result in a lower classification.

In the current draft of the legislation, intermediate chemicals are exempted from testing due to the argument of "non-existing" exposure. In extension of the no-exposure-no-concern concept, Combes and co-workers (2003) suggested integrating a "threshold of toxicological concern" (TTC) concept into the current REACH procedure in order to minimise the need of toxicological testing. The proposed revival of this TTC concept for chemicals regulations (introduced by Frawley in 1967) is based on the premise that toxicity data of a wide range of substances could be used to define a general maximum level of safe exposure which could be applied generally to any new chemical without testing results. If the predicted exposure were less than this level, it might be possible to exempt the substance from legislation. Kroes and Kozianowski (2002) reviewed the concept and expressed the view that up to a daily intake of 1.5 μg per person would be low enough to accommodate all toxicological endpoints. However, there is no consensus on whether this concept could be applicable beyond its original scope: the minimum threshold for dietary consumption, for indirect food additives and food contaminants. From a regulatory standpoint, the approach is attractive, since it would allow for the exclusion of a number of substances from any detailed evaluation. From a technical standpoint, there is no proof whether exposure can really be calculated with the necessary precision from theoretical models.

It may be worthwhile to evaluate some new approaches for registration, e.g. to introduce standard exposure patterns, subsumption of uses, product groupings and volume thresholds to facilitate accurate exposure data for health risk assessment. It should be

kept in mind, however, that a general requirement for accurate exposure identification for all existing chemicals would create a significant financial and organisational burden.

Identifying health hazards by evaluating toxicological test results

Acute systemic toxicity

Acute toxicity testing of chemicals is one of the first studies to be performed for safety management. The results of these studies allow for the estimation of the acute lethal dose (LD50) or concentration (LC50), or a corresponding dose range. In 1999, still every fifth of 700,000 mammals used in toxicity testing in Europe was used for determining this endpoint (EU COM 2003c). Out of 129,000 animals used, about 46,100 could be attributed to medicine, dentistry, veterinary medicine or agriculture. From these figures we estimate that the number of mammals used in acute toxicity testing under the existing chemicals regime in Europe is exceeding 80,000 per year. The procedures for testing acute oral toxic potential of chemicals have been revised during the last years, moving to less animal consumption, from statistically derived lethal doses (LD_{50}, OECD Test Guideline 401) to lethal dose ranges (OECD TG 420 and 423) or to LD_{50} estimates (OECD TG 425). This process is continuing with protocols for acute dermal and inhalative toxicity (Holzhütter et al. 2003; Stallard et al. 2003).

There may be a regulatory requirement for the oral and dermal path of exposure under REACH. However, to reduce the volume of testing, percutaneous application should only be performed if oral toxicity has been detected and dermal toxicity is expected to follow different modes of action. Experience gained under the European notification procedure demonstrates that substances proved harmful or toxic after skin contact only when significant acute oral toxicity and relevant acute irritation potential is observed (Gerner et al. 1994). Therefore, testing acute toxicity by dermal application will in general not contribute to any further knowledge or classification.

Since the early 1990s, the German Centre for Documentation and Evaluation of Alternatives to Animal Testing (ZEBET) evaluated possibilities to use in vitro tests for basal cytotoxicity in order to screen for systemic toxicity potentials and to predict lethal dose ranges and appropriate starting doses for acute systemic toxicity studies (Halle et al. 1997; Spielmann et al. 1999; NIH/ICCVAM 2001a, b; Halle 2003). This activity combined with development of appropriate (Q)SAR methods and the use of existing but unpublished animal testing results will, hopefully, result in comprehensive replacement of animal testing for classification of acute toxicity in the near future.

Irritation and corrosivity

The main areas of potential irritation or corrosion are skin and eyes (including mucous membranes). The corrosivity of inhaled vapour of a chemical is observed during acute or repeated dose inhalation tests. This chapter refers to skin and eye irritation and corrosion only. Irritation or destruction of skin or eyes is a well-known hazard of chemicals and, therefore, as early as the 1940s rabbit tests had been developed by Draize and co-workers (1944). In 1999, tests on skin and eye irritation accounted for about 12,000 mammals in the European Union, in general rabbits (EU COM 2003c). About 50% of these tests had been used in order to assess industrial chemicals. Several alternative in vitro testing systems for assessment of corrosion developed in the early 1980s were validated in the late 1990s by ECVAM (Fentem et al. 1998; Worth et al. 1998; Worth and Cronin 2001) and by the US Interagency Center for the Evaluation of Alternative Toxicological Methods (Federal Register 2001; NICEATM 2001). They have since been integrated into official guidelines (e.g. OECD TG 430, OECD TG 431). At present, acute local irritation potential still has to be tested on animals. The existing OECD testing strategy (evaluated by Worth et al. 1998) excludes Draize tests on skin and eye only in case of severe lesions detected by in vitro systems or extrapolated from pH-data (OECD TG 404, OECD TG 405).

Success in developing and validating alternative tests to fully replace the Draize rabbit eye irritation test has remained elusive despite major efforts including six validation and evaluation studies between 1991 and 1997 (Gettings et al. 1991, 1994, 1996; Spielmann et al. 1993, 1996; Ohno et al. 1994; Balls et al. 1995; Bradlaw et al. 1997; Brantom et al. 1997). Balls et al. (1999) developed recommendations for future work in this area. However, testing for serious eye damaging is already routinely performed using alternative methods, although not formally validated. In vitro tests for discrimination between serious eye damage and moderate eye irritation, however, are not available. There is no validated in vitro test for classifying moderately skin-irritating chemicals. However, there are several pre-validation efforts under the umbrella of ECVAM as summarised by Zuang et al. (2002). An additional validation study by ECVAM has started including Episkin, EpiDerm and SIFT protocols and further prediction models to discriminate irritants from non-irritants. Studies have identified physicochemical properties as being essential for causing significant local irritation (Gerner et al. 2000; Zinke et al. 2000). (Q)SARs may become a suitable tool for the prediction of the absence of relevant local irritation potentials (Gerner and Schlede 2002). Of all chemicals, 30–80% are not irritating or corrosive to the skin. Any new assessment to identify these non-irritating chemicals should not be based on experimental animals to have the maximum reduction in testing. We assume that no significant animal testing for local irritation or corrosion

will be necessary under future European chemicals regulation using a tiered assessment strategy (see Fig. 1).

Sensitisation

The allergic potential of chemicals has become an important aspect in public health, and sensitisation by chemical substances has thus become an important part of the hazard assessment process. We estimate the total number of animals used in Europe per year for those tests under chemicals legislation based on EU data to reach 20,000 (EU COM 2003c). All current toxicological test methods are based on OECD Guidelines using laboratory animals. The Magnusson-Kligman procedure had been used in nearly 90% of these experiments. Recently, a new animal test method using a smaller number of rodents and causing less pain to the test animals, the Local Lymph Node Assay (LLNA), was introduced (OECD TG 429). At present, there is no guideline for the assessment of inhalative sensitisation, which is therefore exclusively classified on the basis of human experience if ever existing. Although the European Commission's Scientific Committee on Cosmetics and Non-Food Products (SCCNFP) pursues the aim of replacing in vivo sensitisation tests with in vitro alternatives within this product range, in 2000 it concluded that no validated in vitro methods were available at that date (SCCNFP 2000, 2003). Concerning human sensitisation tests, the Committee concluded: "The human

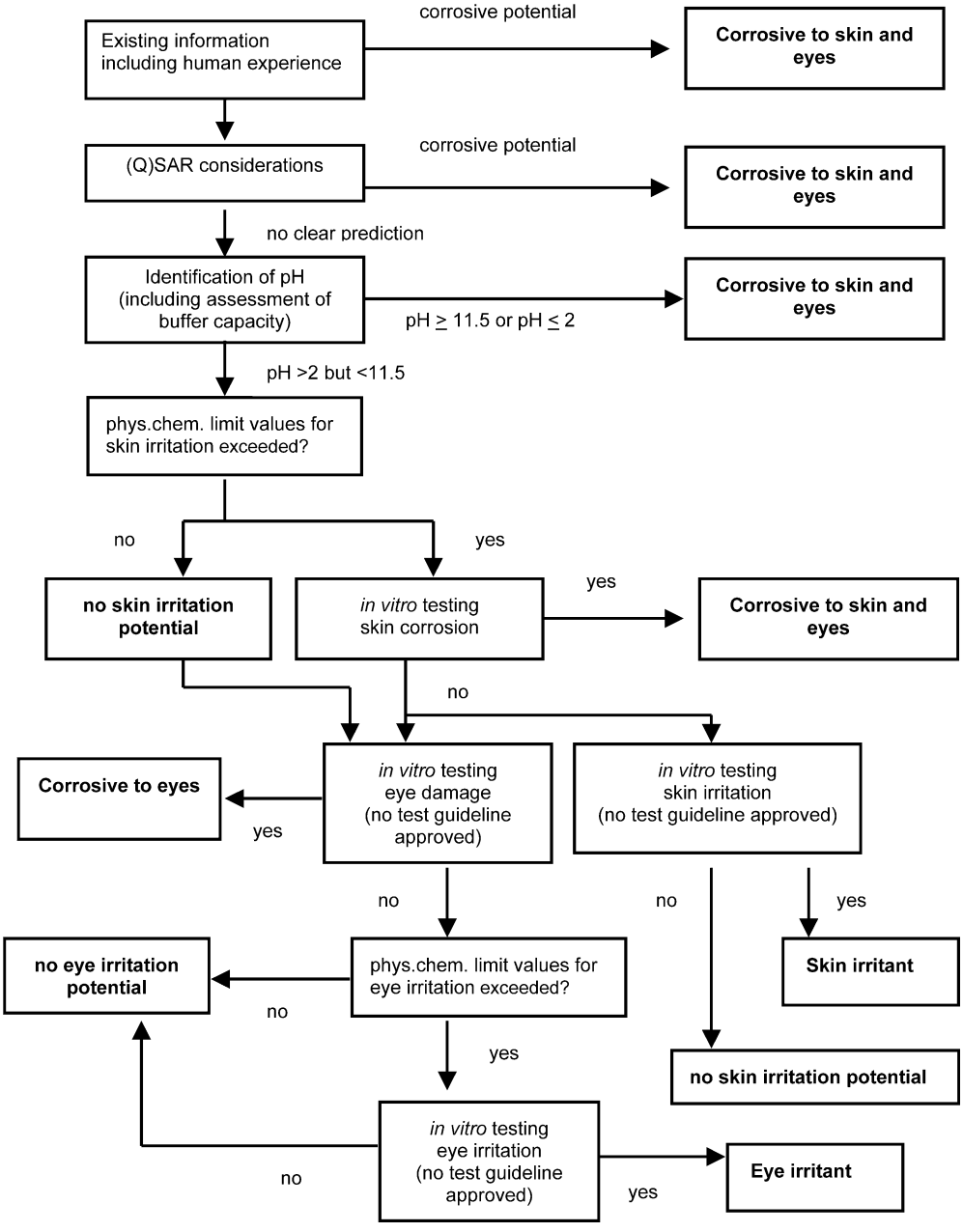

Fig. 1 Example for a future regulatory assessment strategy: acute local irritation/corrosion

sensitisation tests are time consuming and very expensive because a large number of volunteers is required in each test... the selection of human volunteers usually results in the use of an inhomogeneous test group.'' In the near future, skin sensitisation potential may probably be pre-assessed by means of (Q)SAR predictions using ''structural alerts''. Combination with the respective structural alerts used in the expert system DEREK led to publication of two sets of structural alerts for the prediction of skin sensitisation potentials (Gerner et al. 2003).

Target organ/systemic toxicity (repeated dose)

The identification of adverse health effects after repeated or long-term exposure to chemicals is based either on experimental animal studies or reliable human experience. The potential of inducing chronic organ damage or dysfunction, effect doses/concentrations and non-effect doses/concentrations of a substance has to be derived from in vivo experiments. In 1999, relatively few animals (6,513 mammals) were used in subchronic and chronic toxicological tests for substances under chemical regulation (EU COM 2003c). During the last decade, under the EU existing substances programme less than five repeated-dose studies (28 or 90 days) were conducted by industry, indicating that for production ranges above 100 t/a data are existing. For the vast majority of existing substances produced in volumes up to 100 t/a, there is no information about repeated-dose toxicity. Under REACH, a 28-day study will be required for chemicals above a production volume of 10 t/a.

Longer treatment regimens are chosen to cover a greater part of the lifespan of the selected animal or organ system and treatment commences at a relatively young age, ensuring that the growth phase of juveniles is covered. Effects on organs with a regenerating capacity, but a long cell cycle duration, are more adequately covered by long-term experiments (e.g. 90-day test design). Neither the immuno-suppressive effects, impaired maturation on bone marrow progenitor or stem cells nor the associated secondary lesions in other organs (such as lymphoid, gastrointestinal or reproductive system) are detected during 28 days. A red cell life span and the production time of platelets is about 50 days in rats. It is difficult to identify effects on red cells or thrombocytes within shorter periods (Valli et al. 2002). The detection of disturbances of endocrine systems is hampered. To recognise toxic effects on the testis, the treatment period should cover at least the complete process of spermatogenesis, which is 56 days in rats (Creasy 1997). Hyperplasia or dysplasia of target tissue may, in some cases (e.g. urinary bladder carcinogens), indicate a potential for carcinogenic action, which is rarely detected under a 28-day design. Choosing a 90-day study as the primary study on repeated-dose toxicity can thus prevent unnecessary additional animal testing. Further studies on chronic toxicity (≥12 months) may have to be conducted. By interagency and industry co-operation, guidance on a tiered testing strategy on chronic toxicity should be developed. In vitro testing will not be able to replace repeated-dose studies in the near future. In vitro data can improve the understanding of the mode of action underlying the toxic effect (EC TGD 2003). The development of new in vitro techniques is welcomed to improve knowledge and the interpretation of animal data.

The most promising new techniques that are currently being developed and having an impact in this area are toxicoproteomics or toxicogenomics (Corton et al. 1999; Huggins 2003; MacGregor 2003; Merrick and Tomer 2003). Expression analysis tests are internationally discussed for use in regulatory toxicology (Fielden and Zacharewski 2001; Bandara and Kennedy 2002; Tennant 2002; Ramos and Goehl 2003), but not validated. Studies to enlarge the 28-day repeated-dose study by proteomic tools have started (Heinrich-Hirsch et al. 2001; Oberemm et al. 2003).

Mutagenicity

Mutagenicity refers to the induction of permanent transmissible changes in the amount or structure of the genetic material of cells. Genotoxicity is an important toxicological endpoint, in particular in view of the potential carcinogenic effect of mutagens. Mutations may result in alterations in the expression of the gene or the structure of the gene products. The bacterial in vitro test developed by Ames became a standard procedure in the 1970s, testing concentrates on the genotoxic potential. Although the mutagenic potential can be tested in non-animal tests in particular, about 25,100 mammals yearly were used in Europe (EU COM 2003c). We estimate the number of mammals used for testing mutagenicity under the existing chemicals regime to be above 9,000 per year. It should be noted, however, that in vitro mutagenicity tests have shown to be able to identify potential in vivo mutagens. Validated tests and OECD guidelines are available (OECD 2003). Not all detected in vitro mutagens are relevant for the human situation. Therefore, positive results are often questioned by animal tests. In general, routine in vivo tests are conducted with somatic cells (mainly bone marrow cells). Conducting additional germ cell tests is normally not justified. There is no general necessity to perform in vivo mutagenicity tests. It may well be that available toxicokinetic and toxicodynamic data may give sufficient evidence to show whether the substance might pose a genetic hazard or not. In practice, it is of special importance whether a routine bone marrow test is appropriate (only in case of considerable systemic availability) or a so-called local genotoxicity test on specific tissues will give more relevant information (e.g. in case of low systemic availability but high exposure of tissues of first contact). On the basis of such new testing strategies, the number of animal experiments needed under the new chemicals policy will stay low.

Carcinogenicity

The evaluation of the carcinogenic potential of substances is important, as synthetic substances are often held responsible for the high rate of carcinomas in the population. Carcinogenesis is a multi-step process, which occurs through a variety of incompletely understood mechanisms. The assessment of carcinogenicity is based on all available data, animal experiments, human experiences and epidemiology studies. Conventional 2-year rodent studies are still the primary method to identify the carcinogenic potential. In 1999, the number of animals used in cancer bioassays for substances covered under chemical regulation accounted for 2,225 (EU Com 2003c). Assuming that OECD guideline-compliant studies use 400 rats or mice per study, it can be calculated that five studies on carcinogenicity were conducted in the EU in 1999. Within the EU programme on existing chemicals, a cancer bioassay was requested for none out of 141 substances for which risk assessment reports were finished or drafted by June 2003. This situation partly explains the actual low numbers of animals used for carcinogenicity testing despite the large number of chemicals on the market. With a few carcinogenicity tests performed during the last two decades of EU chemicals policy, the knowledge on carcinogenic potential is insufficient for the majority of high volume chemicals and there is a significant need to catch up, independently of the type of legislation introduced.

Carcinogenicity testing using short- or medium-term tests or in vitro tests is currently not able to replace conventional cancer bioassays. Under REACH, carcinogenicity testing will follow a tiered approach considering all other toxicity and exposure data. REACH points out that a carcinogenicity study may only be performed when there is evidence on a widespread use or long-term exposure to humans and there is a specific concern by a positive mutagenic potential or evidence on precursor lesions to neoplasm. This will limit the need for animal testing.

Reproductive toxicity

Reproduction is a continuous cycle in which toxicity testing focuses on two key phases: on the period when male and female fertility could be impaired and on pregnancy in females, when developmental toxicity including teratogenicity could be induced. Despite the complexity of mammalian reproduction, the target tissue or the target organ can be clearly identified in reproductive toxicology. Several standardised OECD Test Guidelines and guideline drafts are available for regulatory purposes. All of these are tests in laboratory animals. A developmental toxicity test requires 150 animals; generation studies consume about 3,200 animals including a high number of offspring. The total number of animals used in Europe for reproductive toxicology testing in 1999 was about 113,000 animals (EU COM 2003c). Nearly 70% of these animals could be attributed to products intended for use in medicine, veterinary medicine, dentistry or agriculture. Animal studies are expensive and will not provide information on the proper mechanism of action. Thus, more specific methods for detecting and studying endocrine effects are urgently needed. (Q)SAR studies have been proposed when estrogen receptor binding is concerned (Tong 1997) but a need for additional in vivo and in vitro screens has been proposed (Gillesby and Zacharewski 1998). In 1997, OECD started an appraisal of test methods for sex hormone disrupting chemicals, which was finished in 2001 (OECD 2001) and which motivated the US Coordinating Committee on the Validation of Alternative Methods (ICCVAM) to invite a peer review panel in 2002 (ICCVAM 2001).

About 20 years ago, the need for more detailed information and the high cost of the two-generation study led to a debate on the use of alternative tests in the field of reproductive toxicology. Due to the complexity of the mammalian reproductive cycle, it is not possible to model the whole cycle in one or two in vitro systems in order to detect chemical effects on mammalian reproduction. But the cycle can be broken down to its biological components which can be studied individually or in combination (Cortvrindt 2003; ECVAM 2003). Several groups tried to establish tests without using animals or at least with reduced animal number. Table 1 shows an overview. These efforts have been reviewed in detail (Villeneuve and Koeter 1993; Brown et al. 1995; Worth and Balls 2002). Taking the progress described into account, the European Centre for the Validation of Alternative Methods (ECVAM) took the lead to manage a conceptual framework in the area of reproductive toxicity. The project "Development of a novel approach in hazard and risk assessment of reproductive toxicity by combination and application of in vitro, tissue and sensor technologies" will be conducted within the 6th Frame Work Program of the European Commission. The project will also cover endocrine effects. Validation of resulting testing procedures is urgently needed for acceptance of the new methods and their implementation into regulatory safety testing. After introducing the new methods, fewer animals will have to be consumed in reproductive toxicity testing, although the number of substances to be tested will markedly increase under proposed REACH concept.

Identifying the need for animal testing under the new EU chemicals policy

Perspectives and projected trends

Although test animal numbers have not been documented in most European countries in detail before 1990, the number of animals used both in research and toxicity testing in Europe increased in the 1950s and 1960s. In the 1970s, the numbers remained unchanged for a few years and have decreased steadily thereafter

Table 1 Some tests proposed to reduce or replace animal experiments in reproductive toxicity

Name of test system	Proposed use as
Embryonic stem cell test (EST)*	Building block in a test strategy in order to replace developmental toxicity testing (OECD TG 414, OECD TG 421)
Whole embryo culture*	Building block in a test strategy in order to replace developmental toxicity testing (OECD TG 414, OECD TG 421)
Micromass test (MM)*	Building block in a test strategy in order to replace developmental toxicity testing (OECD TG 414, OECD TG 421)
Chick embryo retina cell culture	Building block in a test strategy in order to replace developmental toxicity testing (OECD TG 414)
Newborn ovary cultures	Building block in a test strategy in order to replace developmental toxicity testing (OECD TG 414, OECD TG 421)
Human placental perfusion system	Building block in a test strategy in order to replace developmental toxicity testing (OECD TG 414, OECD TG 421)
Analysis of progesterone produced by a modified Leydig Cell line (cLHMR MA 10)	Building block in a test strategy in order to replace one/two generation studies (OECD TG 416, OECD 421)
Testis slices	Building block in a test strategy in order to replace one/two generation studies (OECD TG 416, OECD 421)
Human adrenocortical carcinoma cell line H295R	Building block in a test strategy in order to replace one/two generation studies (OECD TG 416, OECD 421)
Follicle culture bioassay	Building block in a test strategy in order to replace one/two generation studies (OECD TG 416, OECD 421)
Placental microsomal aromatase assay	Building block in a test strategy in order to replace one/two generation studies (OECD TG 416, OECD 421)
Hamster egg penetration test (HEPT)/ hypoosmotic swelling test (HOS)	Building block in a test strategy in order to replace one/two generation studies (OECD TG 416, OECD 421)

*Status: validated

(Höfer-Bosse and Scharmann 1986). In the United Kingdom for example, where high quality statistical data are available, the number of animals declined from about 5.5 million in the 1970s to 3.5 million in the 1980s and to less than 2 million in the late 1990s (Höfer-Bosse and Scharmann 1986; EU COM 2003c). Although a strong general reduction in the use of animals has occurred, this was for the most part due to reduced requirements for medical and pharmaceutical research and development. In 1999, 8.7 million experimental mammals were used in Europe; less than 10% were used for toxicological and other safety-related testing (EU COM 2003c). Of the mammals used, 62% could be attributed to testing for medical, veterinary or agricultural (excluding feed) purposes, which are not covered by regulatory requirements of the EU chemicals policy.

Influence of new strategies in hazard management

When discussing the requirements of testing, the fact that risk management starts with the identification of the intrinsic chemical hazards of a chemical is often ignored. Today, hazard-derived regulations present the majority of regulations, from international transport (with the view on emergencies), via European restrictions in handling of chemicals—to exclude hazardous chemicals from consumer products—down to national precautions against toxic spills to protect the public and the environment. Health hazard classification of chemicals is used to define graduated technical standards for packaging, transport and industrial installations (Höfer and Steinhäuser 2000).

Combes and co-workers (2003) proposed inclusion of exposure-related aspects in order to specify and reduce the need for testing (stage 1 of a tier-testing approach). Although, in principle, this approach is also taken within the White Paper (EU COM 2001), we have not been convinced by this approach and are favouring ''toxicological fingerprints'' characterising the intrinsic properties of chemicals independent of their potential uses. In many cases unforeseen contact in the general public has become known at later stages and accident-related exposure scenarios are not covered, thus reducing any precautionary approach in the transport of potentially toxic products or accidental release from industrial plants. Combes et al. (2003) pointed out that even a full in vitro testing should not be necessary where human exposure is limited by packaging and they proposed that the likelihood of accidental exposure could be estimated and included in the risk assessment. Experts within the competent United Nations committee have already looked for risk-based assessment tools for getting optimised safety levels not based on simple hazard management (see UN TDG 2000; Martínez-Alegría et al. 2003). Up to now, no results have come out of this UN discussion process, and the simple hazard management approach is still preferred. Without any toxicological knowledge, or the assumption of non-expected

exposure because of some measures, no precautions would be enforced. In regulatory hazard management, the so-called downstream regulations are not supported without a ''toxicological fingerprint'' and hence there is a need to identify the intrinsic hazards of chemicals. One approach illustrating this aspect is the revised hazard evaluation procedure of GESAMP, a scientific advisory body of some United Nations specialised agencies, resulting in the GESAMP Hazard Profile GHP (GESAMP 2002). In contrast to the European system of allocating Risk Phrases in case of scientifically proven hazardous properties only, GESAMP includes a full set of hazard ratings as a ''toxicological fingerprint'' characterising a chemical. Ratings derived from tests are well defined, scientifically extrapolated ratings are distinguishable and toxicological gaps that could not be filled are specifically noted. The new legislation should integrate a GESAMP-like approach to allow competent estimation of hazards by experts or (Q)SAR.

Estimates for animal testing needs in Europe

In the first comprehensive study on additional animal testing that will be required according to the first draft of REACH (IEH 2001a) the number of animals that will have to be tested was calculated from the number of chemicals that need to be regulated. From the latest version of the REACH proposal (testing requirements see Table 2), we have estimated the theoretical

Table 2 Toxicological testing needs and procedures under the REACH concept

OECD TG	Type of test	Condition/requirement for testing	Animal test	Yearly production volume of a chemical (tons)			
				1–10	10–100	100–1000	>1000
430, 431	Irritation and corrosion: skin	-	No	x	x	x	x
	Irritation and corrosion: eye	-	No	x	x	x	x
406, 429	Skin sensitisation	None, if irritative, corrosive or highly toxic by dermal route	Yes	x	x	x	x
404	Irritation: skin	None, if acutely toxic by dermal route	Yes	-	x	x	x
405	Irritation: eye	None, if acutely toxic by dermal route	Yes	-	x	x	x
402, 403, 420, 423, 425, 433	Acute toxicity	Two routes (oral, dermal or inhalative) to be tested	Yes	-	x	x	x
407, 410, 412	Target organ systemic toxicity: repeated-dose toxicity 28 day	One route (oral, dermal or inhalative) to be tested; except if 90 days or chronic toxicity is available; OECD TG 410, OECD TG 412 only if strongly justified	Yes	-	x	x	x
408, 409, 411, 413	Target organ systemic toxicity: repeated-dose toxicity 90 day	One route (oral, dermal or inhalative) to be tested; 90-day test alternative to 28 days; none, if 28 days showed severe toxicity; none, if chronic toxicity is available ; OECD TG 409, OECD TG 411 only if strongly justified	Yes	-	-	x	x
471	Mutagenicity: bacterial gene mutations	-	No	x	x	x	x
473	Mutagenicity: in vitro mammalian chromosome aberrations	-	No	-	x	x	x
474	Mutagenicity in vivo	Only if positive in vitro	Yes	-		x	x
421	Reprotoxicity: screening test	None, if genotoxic carcinogen, germ cell mutagen or exposure can be excluded	Yes	-	x	-	-
414	Reprotoxicity: teratogenicity	(x): only, if screening test is positive; x: in any case, except if genotoxic carcinogen, germ cell mutagen or exposure can be excluded	Yes	-	(x)	(x)	x
416	Reprotoxicity: two generations	None, if genotoxic carcinogen, germ cell mutagen or exposure can be excluded	Yes	-	-	x	x
452, 426	Target organ systemic toxicity: repeated-dose toxicity ≥12 months	If severe effects within 28/90 days observed, for which evidence is adequate for toxicological characterisation; if assumed effects not to be detected within 90 days; exposure to be considered; specific toxicological studies to investigate toxicity of particular concern (neurotoxicity, immunotoxicity); OECD TG 426 only if strongly justified	Yes	-	-	-	x
451, 453	Carcinogenicity	If widespread use or long-term exposure and mutagen category 3 or pre-neoplastic lesions during repeated toxicity study	Yes	-	-	-	x

maximum number of animals to be used with each OECD Test Guideline protocol (Table 3).

For conducting the so-called base set of testing with all existing chemicals, the MRC IEH in Lester (UK) estimated in 2001 that about 7.2 million mammals will have to be used, assuming that for 25% of the existing chemicals basic toxicity data have already been generated in the past (IEH 2001a). It was acknowledged that REACH proposes in particular in vitro tests for the base set of testing. However, since at the time of estimation no details were available on how to use the new methods and there was a lack of consensus about applying alternative models, animal tests were taken in the IEH study for the full range of the remaining endpoints to be evaluated. However, these numbers correspond to the maximum theoretical total need that would be generated within 12–15 years, but the number did not include the pups resulting from reproductive toxicity testing. Therefore, to fulfil the requirements of the new chemicals policy, theoretically a maximum use of 500,000–600,000 animals may have to be used every year, compared with the 200,000 animals that are used every year under the existing chemicals legislation.

In its second study taking into account the suitable replacements of some animal tests by in vitro procedures, the IEH (2002) estimated significantly lower animal numbers for the 15-year testing, around 1.2 million. On a yearly basis, this would account for 100,000 laboratory mammals, which is about half of current number of experimental animals reported in the official European statistics (EU COM 2003c).

Although in a recent study of the European Chemicals Bureau ECB (Pedersen et al. 2003) only testing costs were calculated, the basic factors, e.g. the estimated need for performing specific tests (percent of substances to be tested), were published by the ECB on the internet and can be used to extrapolate animal numbers. According to the figures of the ECB, about 600,000 animals will have to be used every year for a 15-year period under REACH policy. However, according to this estimation about 90% of the animals will be used in reproductive toxicity and all of the new-born rodents have been taken into consideration.

To get an impression of the most important factors influencing the overall perspective, we attempted to estimate the reduction potential for each toxicological endpoint taking into consideration the recent studies by Pedersen and co-workers (2003) and the IEH (2001a, 2002). Our estimation (Table 4) is based on two decades of experience under current EU chemicals legislation and our experience in developing and validating non-animal testing procedures. According to our experience, the most important issues are the necessity for long-term rodent tests (including the evaluation of the non-genotoxic carcinogenic potential of substances) and whether in vitro tests will be available in the field of reproductive toxicology. According to our estimation, about 80% of test animals will be used in reproductive toxicology. This high percentage results from new-born rodents in the one- and two-generation studies. Thus, slight variations in reproductive toxicity testing including evaluation or classification strategies will result in significant changes

Table 3 Theoretical extrapolation of a maximum number of animals to be used for all chemicals within 12–15 years (no reduction measures as offered under REACH taken into consideration)

Type of test	Max. number of animals per single experiment (test)	Production volume of a chemical				Comparison
		1–10 t/a	10–100 t/a	100–1,000 t/a	> 1,000 t/a	
		Prognosis for number of chemicals and resulting cumulative number of animals				Actual testing per year in 1999 within the EU
		20,000	4,600	2,900	2,600	
Irritation and corrosion: skin, in vitro	0	-	-	-	-	(in vitro)
Irritation and corrosion: eye, in vitro	0	-	-	-	-	(in vitro)
Skin sensitisation	20	400,000	92,000	58,000	52,000	20,000
Irritation and corrosion: skin, in vivo	3	-	13,800	8,700	7,800	12,000
Irritation and corrosion: eye, in vivo	3	-	13,800	8,700	7,800	
Mutagenicity: cytogenetic in vitro mammalian	0	-	-	-	-	(in vitro)
Mutagenicity: gene mutation mammalian in vitro	0	-	-	-	-	(in vitro)
Acute toxicity (two studies)	2×12	-	110,400	69,600	62,400	83,000
Target organ systemic toxicity: repeated-dose toxicity 28 days	40	-	184,000	161,000	104,000	6,513
Target organ systemic toxicity: repeated-dose toxicity 90 days	80	-	-	232,000	208,000	
Target organ systemic toxicity: repeated-dose toxicity ≥24 months	160	-	-	-	416,000	
Mutagenicity in vivo	70	-	-	203,000	182,000	9,000
Carcinogenicity	400	-	-	-	1,040,000	2,225
Reprotoxicity: screening test	560	-	2,576,000	-	-	57,000
Reprotoxicity: teratogenicity	150	-	690,000	435,000	390,000	
Reprotoxicity: two generations	3,200	-	-	9,280,000	8,320,000	

Table 4 Reduction in number of animal tests using all perspectives for minimising animal testing needs under REACH

Type of test	1–10 t/a	10–100 t/a	100–1,000 t/a	>1,000 t/a
Skin sensitisation	↓↓	↓↓	↓↓	↓↓
Irritation: skin, in vivo	-	↓↓↓	↓↓↓	↓↓↓
Irritation: eye, in vivo	-	↓↓↓	↓↓↓	↓↓↓
Acute toxicity (two studies)	-	↓↓	↓↓↓	↓↓↓
Target organ systemic toxicity: repeated-dose toxicity 28 days	-	↓	↓↓	↓↓↓
Target organ systemic toxicity: repeated-dose toxicity 90 days	-	-	↓	↓↓
Target organ systemic toxicity: repeated-dose toxicity ≥12 months	-	-	-	↓↓↓
Mutagenicity in vivo	-	-	↓↓	↓↓↓
Carcinogenicity	-	-	-	↓
Reprotoxicity: screening test	-	↓	-	-
Reprotoxicity: teratogenicity	-	↓↓↓	↓↓	↓↓↓
Reprotoxicity: two generations	-	-	↓↓	↓↓

Reduction categorised as 10–50% (↓), 50–80% (↓↓) and greater than 80% (↓↓↓). Estimations of the authors taking into consideration the studies by Pedersen (2003) and IEH (2001a, 2002). Theoretical maximum number of animal testing without any reduction is shown in Table 3

Table 5 Estimated numbers of laboratory animals used in Europe under REACH after inclusion of all reduction effects

Number of mammals[a]	IEH (2001a) [b]	IEH (2002) [b]	Pedersen (2003) [b]	Our estimate[c]
Total, including reprotoxicity tests	no data	no data	9.0 Mill	7.5 Mill
total, excluding reprotoxicity tests	7.2 Mill	1.2 Mill	1.1 Mill	1.3 Mill
Per year, including reprotoxicity tests	no data	no data	600,000	498,000
Per year, excluding reprotoxicity tests	500,000	100,000	70,000	88,000

[a]Under the assumption that testing of all chemicals under REACH will be performed within 15 years. The term "excluding reprotoxicity" ignores in particular the estimated numbers of newborn animals under appropriate tests for total estimate

[b]The numbers are not always directly shown in the cited reports and are therefore not authorised figures by these authors. Based on the number of tests or equivalent data published, we calculated average figures based on numbers of animals needed for specific OECD Test Guidelines (as shown in Table 3) and the reduction potentials published in the cited reports

[c]Our own estimates are based on the reduction potentials as shown in Table 4 and following assumption on averages: 40% reduction for ↓, 75% for ↓↓ and 90% for ↓↓↓

in the total number of animals used under the REACH policy.

REACH will provide a better quality of information on the hazards of existing chemicals to humans, while due to improved testing and assessment strategies in comparison to today, the annual numbers of test animals will most probably only double within the next 15 years. If no data were available since not a single chemical had been tested so far and all endpoints would have to be covered by animal experiments (see Table 3), animal numbers would reach 45 million under the REACH policy. We have used the numbers in the reports published by the IEH (2001a, b, 2002) and Pedersen and coworkers (2003) to calculate the total number of animals required under the REACH policy (Table 5). Between the first and the second study of the IEH, the estimated number of test animals (excluding reproductive toxicity) was reduced from 7.2 to 1.2 million. The lower value is confirmed by our evaluation and the report of Pedersen et al. (2003) taking into account our data on animal need for specific OECD Test Guidelines (see Table 3). New testing requirements under the REACH policy will have an impact on companies outside Europe and testing will be performed in those countries. Since the number of animal experiments that are performed by European companies outside the EU today is unknown, in this respect our impact assessment is limited.

Uncertainty of estimating the need for animal tests

Estimates of the future requirements of laboratory animals under the REACH policy depend on assumptions and uncertainties. The most important problem is derived from unpublished tests that have already been conducted by industry. Although companies often claim that their products are safe, industry studies on business impact of the REACH policy usually assume that for almost all of the existing chemicals, testing will have to be conducted for all endpoints of toxicity (EU COM 2003e). Such declarations are, of course, biased, since for reasons of both occupational safety and liability, a basic set of testing has usually been conducted by industry. The second assumption concerns the result of the potential future use of toxicological non-animal testing procedures. The third assumption concerns the impact of the ongoing development of new technologies in the life sciences and their impact on regulatory toxicology. New techniques have been introduced and their potential cannot clearly be estimated today (e.g. toxicogenomics, proteomics, the use of transgenic animals and their cell lines, stem cells). There are a number of in vitro methods ready for evaluating the toxic properties of chemicals. The impact of the co-operation between industry and various regulatory authorities in designing tailor-made testing strategies cannot be predicted and it

may take more than a decade until "precautionary" labelling based on common sense and scientific judgement will be accepted. Under the REACH policy, toxicologists from international regulatory agencies will have to be involved in accepting complex test designs, whereas today most experts are asking for more basic research.

The international influence on the needs for animal testing

An important aspect that has to be taken into account is the globalisation of both chemical companies and safety testing. Even if the European Union would not ask for animal experiments, a number of international regulations may require testing in animals. Globally acting companies have to respond to these requirements due to their worldwide activities. The new REACH chemicals policy, which may have an important impact even outside Europe, has to be evaluated in this context. The worldwide harmonisation of toxicological testing by the OECD guidelines and the harmonisation of classification criteria under the auspices of the United Nations are important factors driving the development of modern (Q)SAR and in vitro methods in order to meet globally agreed classification criteria. All new testing alternatives and toxicological endpoints for in vitro testing procedures have to be accepted and introduced within this international scenario. If these criteria are not met, the chemical industry will continue to conduct testing according to existing guidelines, even if they are not required by EU legislation. This aspect will have an important impact on animal testing in Europe for regulatory purposes. At the international level labelling as well as other hazard related classification, e.g. transport and industrial plant license regulations, have significant economic effects since they are setting the stage for the technical requirements of packaging and of the safety features of plants for production or storage. In comparison to the costs involved, animal experiments are not expensive and they may even offer a perspective for less severe safety requirements, if a lower hazard classification class can be proven. Thus, animal testing will continue under the new EU chemicals policy, although it is not appreciated under the current European animal welfare regulation, since chemicals evaluation that is based on non-animal screens tends to stay on the safe side and leads to more conservative classification and labelling.

Time frame for implementing the new EU chemicals policy

The draft proposal of the new EU chemicals directive has set a specific time frame for assessing the properties of existing chemicals. This includes the regulatory acceptance of validated new testing strategies and testing according to tailor-made programmes for individual chemicals. In order to use non-animal testing methods most efficiently, intensive research will be required during a very short time frame since the methods will have to be implemented into regulatory testing. Taking into account these scientific constraints, the proposed deadlines for implementing the proposed REACH policy seems very ambitious.

Conclusions

We have identified six main factors in our evaluation that will have an impact on reducing test animal numbers under the proposed REACH policy for chemicals testing in Europe:

1. Research priorities and resources for funding: risk assessment including classification and labelling must rely on appropriately validated testing procedures, while formal validation is not of importance, when methods are used for priority setting. There is no doubt that within the time frame set for implementing the REACH policy, without major funding there will not be a sufficient number of validated non-animal tests established.
2. Integrated testing strategy: testing of several thousands of chemicals will be necessary to satisfy the evaluation requirements of the new European chemicals policy. However, an integrated testing strategy would minimise the use of animals as well as of the costs involved. Several integrated stepwise testing strategies have already been developed and proposed to be used for regulatory purposes. Figure 1 shows an example of an integrated testing strategy for assessing the skin and eye irritation/corrosion potential of chemicals. Such new assessment strategies will also have to undergo formal evaluation and validation.
3. Tiered testing programme: the absolute numbers of repeated-dose studies in experimental animals will definitely increase. However, the increase of numbers of studies is expected to be moderate because the stringent current testing program will be replaced by a substance-tailored testing design, which allows for more flexibility. The tailor-made testing requirements will have the greatest influence on the future need of animal experiments, in particular for long-term hazards including non-genotoxic carcinogenicity and for the use of non-animal tests in reproductive toxicology.
4. Use of existing data: the handling of existing data, either publication of confidential studies or the criteria-guided acceptance of non-guideline studies by risk assessors, will have a great impact on the need for animal experiments. Evaluation of all existing data could also be used for the development and validation of (Q)SARs, which may be combined

within computerised toxicological expert systems for predicting chemical hazards.

5. Estimated classification and labelling: the official acceptance of simple structure-activity-related techniques, like "read-across" or the "expert systems" discussed above, could allow a reduction in the number of individual chemicals to be tested. A precautionary classification and labelling that allows us to estimate risk and safety phrases based on extrapolation logics should be introduced into the regulatory system.
6. Role of UN and OECD: the global harmonisation of the criteria for the evaluation and classification of chemicals by the competent United Nations committee and the publication of validated non-animal test guidelines by OECD will motivate industry to follow the fundamental principles outlined in the EU REACH policy, by implementing more specific testing and assessment strategies and by applying non-animal testing in particular.

It is important that the future EU chemicals policy has a vision beyond the limitations of toxicological science today. However, the EU chemicals policy must in the first place be focussed on protecting and improving the quality of human health and of the environment and secondly on the reduction of animal experimentation and on regulating as many chemicals as possible appropriately. In addition, policy must provide funding of applied research to implement the new chemicals policy and to limit testing in animals concurrently.

Acknowledgements The authors would like to thank Michael Kunde, Stephan Madle, Axel Oberemm and Hans-Bernhard Richter-Reichhelm for their valuable contributions and review of the first draft.

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Presseveröffentlichung des BfR 18/2003 vom 22.07.2003

Geplantes Europäisches Chemikaliensystem bringt Fortschritte für den gesundheitlichen Verbraucherschutz

BfR hält deutliche Nachbesserungen im REACH-System aber für erforderlich

Chemikalien finden sich in vielen Produkten, die den Verbraucher täglich umgeben. Etwa 30.000 chemische Stoffe werden in Mengen von mehr als einer Tonne pro Jahr hergestellt. In welchen Produkten diese Chemikalien Verwendung finden, ist nur zum Teil bekannt. Bewertungen im Hinblick auf mögliche gesundheitliche Risiken liegen nur für einen geringen Prozentsatz der 30.000 Substanzen vor. Dieser unbefriedigende und mit möglichen Sicherheitslücken verbundene Zustand soll geändert werden. Dazu hat die Europäische Kommission einen Verordnungsentwurf vorgelegt, der Einzelheiten zu den Bausteinen Registrierung, Evaluierung, Autorisierung und Verwendungseinschränkung von Chemikalien enthält und deshalb kurz als "REACH-System" bezeichnet wird. Zentraler Punkt sind die Einführung einer einer Zulassungspflicht und ein beschleunigtes Bewertungsverfahren. Auf einer Pressekonferenz des Verbraucherzentrale Bundesverbandes (vzbv) zur EU-Chemikalienpolitik bezeichnete die Leiterin der Chemikalienbewertung am Bundesinstitut für Risikobewertung den Verordnungsentwurf heute grundsätzlich als wichtigen Beitrag zur Chemikaliensicherheit. "In wichtigen Bereichen", so Professor Dr. Ursula Gundert-Remy, "benötigen wir aber dringend Nachbesserungen, um den gesundheitlichen Verbraucherschutz in ausreichendem Maß sicherzustellen".

Mit dem REACH-System soll das Wissen um Einsatz und potentielle Risiken von Chemikalien binnen zwölf Jahren deutlich verbessert werden. Veränderte Zulassungs- und Prüfbedingungen sollen mehr Verbraucherschutz gewährleisten. Neu ist unter anderem der öffentliche Zugang zu den derzeit teilweise nur den Herstellern bekannten Informationen zu Chemikalien; damit erhöhen sich Kenntnisstand und Transparenz zum Nutzen für den Verbraucher. Einbezogen in das REACH-System ist auch die Verwendung von Chemikalien in Produkten. Ebenso wie die Hersteller muss die weiterverarbeitende Industrie ihrer Informationspflicht nachkommen und nachweisen, dass keine für Umwelt und Gesundheit bedenklichen Erzeugnisse in den Verkehr gebracht werden. In das System einbezogen sind außerdem die Importeure von chemischen Substanzen und Erzeugnissen.

Konkret sieht das Konzept vor, Daten zu toxikologischen und ökotoxikologischen Eigenschaften sowie zum Verwendungszweck von gut einem Drittel der 100.000 auf dem Markt befindlichen Chemikalien zu erheben. Die Anforderungen an den Umfang der Information sind produktionsmengenabhängig gestaffelt. Mehr als 60.000 Stoffe bleiben von der Regelung aufgrund geringer Produktionsvolumen unberührt (vgl. bgvv-Pressedienst 10/2001 vom 2. März 2001).

Für Stoffe mit krebsauslösender, erbgutschädigender oder Fortpflanzung bzw. Nachkommen beeinträchtigender Wirkung schreibt das REACH-System ein Zulassungsverfahren (Autorisierung) vor, in dem Verwendungszwecke eingeschränkt und festgeschrieben werden. Informationen und vorhandene Daten zu Stoffen mit Produktionsmengen über einer Tonne müssen innerhalb bestimmter Fristen an eine zentrale europäische Agentur gegeben werden.

Das BfR begrüßt den Verordnungsentwurf und das zugrundeliegende REACH-System grundsätzlich: Die vorgeschlagenen Maßnahmen versprechen für den Umweltschutz wichtige Verbesserungen. Um aber auch den Verbraucherschutz hinreichend zu gewährleisten, sind aus Sicht des BfR deutliche Nachbesserungen erforderlich. Das gilt insbesondere für die Zulassung der Chemikalien. Autorisiert werden müssen nach dem Verordnungsentwurf nur chemische Stoffe, für die eine Gefährdung durch krebsauslösende, erbgutschädigende oder Fortpflanzung bzw. Nachkommen beeinträchtigende Wirkungen erwiesen ist. Nach An-

sicht des Bundesinstituts für Risikobewertung muss die Zulassung zwingend auch auf die chemischen Stoffe ausgedehnt werden, für die bislang nur Hinweise auf diese Wirkungen vorliegen. Aus Gründen des vorsorgenden Verbraucherschutzes sollten auch sie einer intensiven Nutzen-Risiko-Betrachtung unterzogen werden.

Die im Verordnungsentwurf vorgegebenen Fristen lassen einen ehrgeizigen Zeitplan erkennen. Unternehmer, Anwender, Importeure und auch die Behörden sind gefordert. Derzeit fehlen in dem Verordnungsentwurf allerdings noch Sanktionsmaßnahmen, um sicherzustellen, dass dieser Zeitplan auch eingehalten wird. Nach Ansicht des Bundesinstituts für Risikobewertung hat der Verbraucher ein Recht darauf zu wissen, welche Stoffe ihn umgeben und in den Produkten enthalten sind, die er täglich anwendet. "Dieses Recht", so Ursula Gundert-Remy, "muss heute eingelöst werden, nicht erst für zukünftige Generationen".

ende bfr-p
Pressedienste

Dortmund und Berlin, den 20. September 2004

Bundesanstalt für Arbeitsschutz und Arbeitsmedizin

Umweltbundesamt

Bundesinstitut für Risikobewertung

Das Konzept "Verwendungs- und Expositionskategorien" – Standpunkt der deutschen Bewertungsbehörden September 2004

1) Einleitung

Stoffe als solche, z.B. Cadmium oder Aceton, Stoffe in Form von Gemischen, z.B. Autolacke oder Klebstoffe, und Stoffe als Bestandteile von Fertigerzeugnissen, z.B. in Autos oder Zeitungen, werden in vielfältiger Art und Weise hergestellt und verwendet. Sie kommen dabei während ihres Lebenswegs – von ihrer Herstellung über ihre Ver- oder Anwendung und ihre Nutzung in Erzeugnissen (engl. service life) bis hin zu ihrer Entsorgung – auf unterschiedliche Art und Weise mit Mensch und Umwelt in Berührung. Diese Exposition von Mensch und Umwelt kann dabei zu gewünschten, ebenso wie zu unerwünschten Effekten führen. So schützt z.B. eine witterungsbeständige Lackierung Material vor Verrottung oder Korrosion; andererseits wird das behandelte Material nach seinem Gebrauch vermutlich schwer biologisch abbaubar oder kaum wiederverwendbar sein. Das generelle Ziel einer nachhaltigen Produktionsweise sollte es daher sein, die Eigenschaften und die Verwendung eines Stoffes so zu gestalten, dass der Nutzen realisiert werden kann und gleichzeitig die Exposition von Mensch und Umwelt über den gesamten Lebensweg in der Weise begrenzt wird, dass möglichst keine oder nur geringe nachteilige Auswirkungen auftreten. Mit der geplanten REACH-Verordnung [1] werden Hersteller und Importeure von Stoffen sowie nachgeschaltete Stoffanwender (engl. downstream user) für die Sicherheit ihrer Stoffe und Erzeugnisse verantwortlich gemacht.

Vor dem Hintergrund der Tatsache, dass nach der geplanten REACH-Verordnung rund 30.000 Stoffe und ihre unterschiedlichen Einsatzgebiete in vielen verschiedenen Produktarten, wie Möbellacken, Autolacken, Spielzeug, Klebstoffen, Papier, Waschmitteln, Kosmetika, sowie die unterschiedlichsten Anwendungen dieser Stoffe und Produkte bewertet werden sollen, hat die Bundesregierung in der „Gemeinsamen Bewertung mit VCI und IG Bergbau, Chemie und Energie“ vom 21. August 2003 eine Expositionsbeurteilung auf der Grundlage von **Verwendungs- und Expositionskategorien (VEK)** im Rahmen eines gestuften Ansatzes vorgeschlagen [2]. Die VEK sollen die Kommunikation in der Wertschöpfungskette vereinfachen und die Expositionsbeurteilung für die Stoffanwender handhabbarer machen. Dabei muss jedoch weiterhin Unternehmen wie Behörden die Möglichkeit

einer Einzelfallbetrachtung für diejenigen Situationen offen bleiben, bei denen eine Kategorisierung zu Problemen führt.

Der Erfolg der REACH-Verordnung wird aus Sicht der deutschen Bewertungsbehörden BAuA[1], UBA[2] und BfR[3] in hohem Maße davon abhängen, wie die technische Umsetzung der Stoffsicherheitsbeurteilung und hier vor allem diejenige der Expositionsbeurteilung gelingt, und wie anschließend die Ergebnisse der Risikobeschreibung in der Wertschöpfungskette kommuniziert werden. Nur wenn eine allgemein verständliche und transparente Anleitung zur Expositionsbeurteilung im Prozess der technischen Umsetzung von REACH erarbeitet wird, werden die Verantwortlichen, d.h. die Hersteller und Importeure von Chemikalien sowie die nachgeschalteten Stoffanwender, ihren Pflichten nachkommen können.

Derzeitige Grundlage der Expositionsbeurteilung ist das EU Technical Guidance Document on Risk Assessment (EU TGD, 2003) [3], das bereits versucht, die Vielzahl der Stoffverwendungen bei der Ermittlung der Exposition zusammenzufassen. Auf dieser Grundlage sollen VEK entwickelt werden mit dem Ziel, die Expositionsbeurteilung für die Stoffanwender einfach und verständlich zu machen.

2) Ziele

Kernziel in der technischen Umsetzung der Stoffsicherheitsbeurteilung in REACH sollte es sein, die Vielzahl der Verwendungsarten von Chemikalien so weit wie möglich zusammenzufassen (zu kategorisieren), um eine für alle Beteiligten durchführbare Expositionsbeurteilung zu ermöglichen. Gleichzeitig muss eine solche Zusammenfassung von Verwendungsarten aber spezifisch und transparent genug sein, um die erforderliche Sicherheit und damit ein hohes Schutzniveau für Mensch und Umwelt zu gewährleisten.

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[1] Bundesanstalt für Arbeitsschutz und Arbeitsmedizin (BAuA), Dortmund

[2] Umweltbundesamt (UBA), Berlin

[3] Bundesinstitut für Risikobewertung (BfR), Berlin

Mit der Einführung von VEK soll insbesondere

- den Stoffanwendern ein einfach zu handhabendes Instrumentarium für die Expositionsbeurteilung zur Verfügung gestellt,
- die Kommunikation in der Wertschöpfungskette unterstützt und erleichtert,
- der Offenlegung von Betriebs- und Geschäftsgeheimnissen, insbesondere der Stoffanwender, vorgebeugt und
- Kosten und Aufwand für eine Registrierung im Rahmen von REACH minimiert werden.

3) Anforderungen an ein System von Verwendungs- und Expositionskategorien

Damit ein System von Verwendungs- und Expositionskategorien (VEK) adäquat ausformuliert werden kann, muss Klarheit über die Anforderungen bestehen, denen ein solches System genügen muss. Diese Anforderungen ergeben sich aus den Zielen, die mit einem solchen System verfolgt werden. Was also soll ein solches System leisten und was nicht? Und welche Eingangsbedingungen ergeben sich daraus?

- Die VEK beschreiben die Bedingungen, unter denen ein sicherer Umgang eines Stoffes in einer Anwendung oder in einem Produkt gewährleistet ist.
- Für die Charakterisierung einer Wertschöpfungskette sind i.d.R. mehrere VEK erforderlich.
- Wenn VEK branchenorientiert entwickelt werden, erleichtern sie den Dialog zwischen Herstellern/Importeuren und Stoffanwendern.
- VEK müssen Parameter zur Verfügung stellen, welche die quantitative Schätzung des Expositionserwartungswertes ermöglichen.
- Die zur quantitativen Schätzung verwendeten Modelle müssen so einfach wie möglich sein und flexible Verfahren zur Emissions- und Expositionsminderung für den Stoffanwender bereitstellen.
- Die Schätzung des Expositionserwartungswertes innerhalb von VEK erfolgt auf der Basis von Standardexpositionsszenarien.

- VEK müssen für den gesamten Lebenszyklus und für die relevanten Eintragspfade eines Stoffes erstellt werden.
- Das System der Expositionsbeurteilung muss für Hersteller, Importeur und nachgeschalteten Stoffanwender das gleiche sein (d.h. kein Systemwechsel entlang der Wertschöpfungskette).
- Durch die Expositionsbeurteilung muss das aktuelle Schutzniveau für Mensch und Umwelt zumindest erhalten, ggf. verbessert werden.
- VEK müssen Vorschläge für Schutz- und Emissionsminderungsmaßnahmen enthalten.

Damit können VEK wie folgt definiert werden:

> *Verwendungs- und Expositionskategorien (VEK) fassen die Expositionssituationen zusammen, die durch vergleichbare Verwendungsarten/-Tätigkeiten und einen bestimmten Satz von Parametern charakterisiert sind. VEK stellen damit eine Zusammenfassung von vergleichbaren Einzelfall-spezifischen Expositionsszenarien dar. Dadurch soll die Gesamtheit der Bedingungen beschrieben werden, welche die Exposition des Stoffes bestimmen.*

Vor dem Hintergrund der in der Praxis in verschiedenen Lebenszyklusphasen[4] der Stoffe zu beobachtenden Expositionssituationen berücksichtigen VEK die folgenden Parameter, die im Anschluss weiter erläutert werden:

1. Eintragspfad in die Umwelt: Luft, Wasser, Boden oder Abfall
2. Aufnahmewege des Menschen (Arbeitnehmer, Verbraucher): oral, inhalativ und dermal
3. Expositionsdauer: kurzfristig oder einmalig, gelegentlich, langfristig oder wiederholt
4. Expositionsort

[4] In der Expositionsbeurteilung werden die folgenden Lebenszyklusphasen eines Stoffes betrachtet: Herstellung, Formulierung, industrielle Anwendung, gewerbliche Anwendung, Verbraucherverwendung, Nutzung in einem Artikel oder Produkt (engl. service life), Wiederverwendung und Abfallentsorgung.

5. Stoffeigenschaften
6. Stoffmenge/Emissionsfaktor
7. Art der Tätigkeit/Verwendungsart
8. Expositionserwartungswert
9. Akzeptable Expositionshöhe (Expositionszielgröße)
10. Schutz- und Emissionsminderungsmaßnahmen

Zu 1. Eintragspfad in die Umwelt

Eine Unterscheidung der verschiedenen Eintragspfade eines Stoffes in die Umwelt beschreibt schematisch, auf welche Art und Weise ein Stoff in die Umwelt gelangt, und über welches Umweltmedium er dann mit Menschen, Tieren und Pflanzen in Kontakt kommt oder kommen kann. Hierbei werden Luft, Wasser, Boden, Biota und Abfall berücksichtigt.

Zu 2. Aufnahmewege des Menschen

Eine Betrachtung der verschiedenen Aufnahmewege (oral, inhalativ, dermal) ist erforderlich, um die sich aus den unterschiedlichen Kontaktformen ergebenden Gefährdungspotenziale und daraus abzuleitende Schutzmaßnahmen ermitteln zu können. So kann beispielsweise der Hautkontakt mit einem Stoff relativ risikoarm sein, wohingegen derselbe Stoff oral aufgenommen toxisch wirkt.

Zu 3. Expositionsdauer

Die Dauer der Exposition spielt für die Ermittlung des Expositionserwartungswertes eine wichtige Rolle. Die Stoffeigenschaften unterscheiden hinsichtlich akuter und chronischer Wirkungen. Dementsprechend muss zwischen kurzfristiger oder einmaliger, gelegentlicher und langfristiger Exposition unterschieden werden. Die Expositionsdauer wird i.d.R. in Tagen pro Jahr angegeben.

Zu 4. Expositionsort

Für die Exposition der Umwelt und die indirekte Humanexposition ist der Ort der Emission wichtig, z.B. lokale oder regionale (diffuse) Emission. Dies ergibt sich hinsichtlich des Umweltschutzes aus der unterschiedlichen Empfindlichkeit von Ökosystemen gegenüber dem Eintrag von Stoffen sowie der möglichen

Interaktionswirkung mit klimatischen und anderen Umweltcharakteristika (z.B. Verteilungs- und Abbauverhalten).

Zu 5. Stoffeigenschaften

Es gibt eine Reihe von Stoffeigenschaften, die für die Expositionsbeurteilung in den drei Schutzbereichen unabdingbar sind. Das sind v.a. das Molgewicht, die Wasserlöslichkeit, der Dampfdruck und der n-Oktanol/Wasser-Verteilungskoeffizient sowie das Staubungsverhalten.

Zu 6. Stoffmenge/Emissionsfaktor

Mit Hilfe von Emissionsfaktoren wird die Stoffmenge berechnet, die von der in den Verkehr gebrachten Menge in die Umwelt oder in Kontakt mit dem Menschen gelangt. Emissionsfaktoren können Ergebnisse von experimentellen Untersuchungen (Messungen) sein, sie können empirisch durch Experten ermittelt werden. Eine wichtige Grundinformation für die Ermittlung des Expositionserwartungswertes ist der Anteil der Stoffmenge, der bei einer bestimmten Anwendung oder aus einem bestimmten Produkt freigesetzt werden kann.

Zu 7. Art der Tätigkeit/Verwendungsart

Die Tätigkeit/Verwendungsart stellt eine wichtige Grundgröße für die Ermittlung des Expositionserwartungswertes dar. Die Vielfalt der möglichen Tätigkeiten/Verwendungen soll dabei nach ihrem Expositionspotenzial strukturiert werden.

Zu 8. Expositionserwartungswert

Der Expositionserwartungswert ist diejenige Expositionshöhe, die bei einer bestimmten Tätigkeit/Verwendungsart erfahrungsgemäß erreicht wird. Der Expositionserwartungswert soll anhand einfacher Modelle auf der Grundlage der expositionsrelevanten Parameter ermittelt werden.

Zu 9. Akzeptable Expositionshöhe (Expositionszielgröße)

Die akzeptable Expositionshöhe ist diejenige Expositionshöhe, die keine unerwünschten Effekte auf Mensch oder Umwelt erwarten lässt. Sie wird mit dem Expositionserwartungswert abgeglichen.

Zu 10. Schutz- und Emissionsminderungsmaßnahmen

Die Charakterisierung einer Verwendung mittels VEK erlaubt es zielgerichtet, die erforderlichen Schutzmaßnahmen zu ermitteln, auf die sich die jeweiligen Expositionserwartungswerte beziehen. Dies können entweder technische Vorkehrungen wie geschlossene Systeme, Absaugung, Abwasser- oder Abfluftreinigung, Abfallbehandlung, Wiederverwendung, Kreislaufführung oder die Verringerung der Konzentrationen des Stoffes in Produkten sein. Maßnahmen-empfehlungen können allgemein oder beispielhaft sein. Der Stoffanwender soll in die Lage versetzt werden, die vorgeschlagenen Maßnahmen nach Prüfung auf ihre Relevanz für seine Verwendung zu übernehmen oder andere, adäquate Maßnahmen zu ergreifen.

4) Optionen zur Anwendung der Verwendungs- und Expositionskategorien

VEK sollen **das Instrument für die Informationsübermittlung** in der Wertschöpfungskette werden. Die Stoffhersteller können die bekannten Verwendungen kategorisieren. Nur so kann die Vielzahl der Stoffe und ihre zahlreichen Anwendungen bewertet werden. Durch Übermittlung der VEK und der damit berücksichtigten Elemente wird der Stoffanwender in die Lage versetzt, auf der Grundlage eines Vergleichs seiner Anwendung mit der VEK zu erkennen,

- ob seine Verwendung mit der VEK übereinstimmt,
- ob er ggf. eine Modifikation der Expositionsbeurteilung vornehmen muss,
- ob und welche Maßnahmen er ergreifen muss.

VEK sollen in einem Stufensystem (engl. tiered system) aufgebaut werden:

Stufe 1: Generische Expositionsabschätzung: robuste einfache Berechnung unter Verwendung von Default-Werten, beispielhafte Maßnahmen-empfehlungen

Stufe 2: Verfeinerung: verfeinerte Berechnung mit erweitertem Datensatz, weitere Maßnahmen, branchenspezifische Informationen

Stufe 3: Spezifischere Expositionsabschätzung: Berücksichtigung von spezi-fischeren Anwenderdaten und Schutzmaßnahmen, aufwändige Berechnung mit ausführlichem Datensatz.

Wenn der Expositionserwartungswert in einer Stufe niedriger liegt als die akzeptable Expositionshöhe, sind keine weiteren Berechnungen mehr notwendig.

Das vorgestellte System der VEK ermöglicht es, die Vielzahl der Verwendungsarten von Chemikalien weit zusammenzufassen. Es wird als Unterstützungsinstrument für die Informationsweitergabe in der Handelskette angesehen. Insbesondere für den Stoffanwender sollen die VEK einfach nachvollziehbare und nachprüfbare Informationen bereitstellen. REACH sieht eine iterative Expositionsbeurteilung vor, an deren Ende die Elemente der VEK sowie die Schutz- und Emissionsminderungsmaßnahmen für eine Verwendung so gewählt sind, dass der Expositionserwartungswert niedriger liegt als die akzeptable Expositionshöhe. Damit enthalten VEK alle notwendigen Informationen für Stoffanwender, die Bedingungen des sicheren Umgangs zu erkennen und in ihrem Bereich umzusetzen.

5) Technische Umsetzung

Zur technischen Umsetzung des Konzeptes der VEK wird vorgeschlagen, ein computergestütztes Programm einzusetzen. Die Basis für dieses System bilden die VEK. Die jeweiligen Expositionserwartungswerte werden auf der Grundlage von Standardexpositionsszenarien per Modell ermittelt. Der Hersteller/Importeur erstellt eine Expositionsbeurteilung für die von ihm identifizierten Verwendungen. Der Stoffanwender muss dann prüfen, ob die angegebenen Bedingungen für ihn zutreffen. Wenn dies nicht der Fall ist, ist das System so gestaltet, dass er mit nur wenigen Daten die Angaben des Herstellers/Importeur verändern kann und somit die relevanten Bedingungen für seine Verwendung oder sein Produkt ermitteln kann. Dazu gehören auch Maßnahmenoptionen.

Neben der Erarbeitung von VEK sind Leitfäden notwendig, welche die Hersteller, Importeure und nachgeschalteten Stoffanwender zu einer für ihre Verwendungen angemessenen und "richtigen" VEK führen. Ein Ansatzpunkt hierfür kann eine Kombination der *Industrial* und *Use Categories* und der *Consumer Product Categories* des EU TGD (2003) [3] bilden. Weitere Klassifikationssysteme für Verwendungen von Stoffen (z.B. Nordic Product Register Database SPIN, NACE

Code der EU, Combined Nomenclature (CN) etc.) sollen für die Bildung der VEK geprüft werden. Eine Anleitung zur Bildung von VEK hinsichtlich der drei Schutzbereiche ist im anstehenden „REACH Implementation Process“ (RIP) unter Beteiligung von Experten der Hersteller, Stoffanwender und Behörden zu erstellen.

6) Literaturangaben

[1] Vorschlag für eine Verordnung des Europäischen Parlaments und des Rates zur Registrierung, Bewertung, Zulassung und Beschränkung chemischer Stoffe (REACH), zur Schaffung einer Europäischen Agentur für chemische Stoffe sowie zur Änderung der Richtlinie 1999/45 und der Verordnung (EG) {über persistente organische Stoffe} vom 29. Oktober 2003.
http://europa.eu.int/comm/enterprise/reach und
http://www.umweltbundesamt.de/reach/reach.htm (englisch und deutsch)

[2] Gemeinsame Bewertung der Bundesregierung, des Verbandes der Chemischen Industrie e.V. (VCI) und der Industriegewerkschaft Bergbau, Chemie, Energie (IG BCE) des Konsultationsentwurfs der Europäischen Kommission für die Registrierung, Evaluation, Zulassung und Beschränkung von Chemikalien (REACH) vom 21. August 2003.
http://www.umweltbundesamt.de/reach/entwicklung-reach.htm

[3] Technical Guidance Document (TGD) on Risk Assessment in support of Commission Directive 93/67/EEC on Risk Assessment for new notified substances, Commission Regulation (EC) No 1488/94 on Risk Assessment for existing substances, Directive 98/8/EC of the European Parliament and of the Council concerning the placing of biocidal products on the market. 2003.
http://ecb.jrc.it/cgi-bin/reframer.pl?A=ECB&B=/tgdoc/

Anlagen: Beispiele

Das o.a. Konzept zur Expositionsbeurteilung, welches das Instrument „Verwendungs- und Expositionskategorie (VEK)“ anwendet, soll an Hand einfacher Beispiele verdeutlicht werden.

(a) Beispiel aus dem Verbraucherschutz: Produkt Innenfarbe

An Hand der akuten Exposition soll hier gezeigt werden, wie ein solches Szenario textlich beschrieben werden kann und welche Daten für die Schätzung erforderlich sind. Im Zusammenhang mit dem REACH Prozess ist auf Einfachheit und Transparenz des Verfahrens besonderen Wert zu legen. Komplexe Darstellungen sollten vermieden und die Szenarienbeschreibungen auf die grundlegenden Fragen beschränkt werden.

Beschreibung des Szenarios:
Es werden 15 kg Farbe auf eine Fläche von ca. 100 m² aufgetragen. Dies entspricht der Wandfläche eines ca. 30 m² großen Zimmers. Die Anwendung erfolgt als einmaliges Ereignis, die Dauer ca. 4 Stunden. Die Exposition erfolgt inhalativ. Eine dermale Exposition erfolgt dadurch, dass beim Streichen, Rollen oder Sprühen von Farbe Farbspritzer auf die Haut gelangen erfolgen kann. Eine orale Exposition müsste für den Fall berücksichtigt werden, dass Kinder als Begleiter mitexponiert sind ("mouthing behaviour").

Die für die Schätzung verwendeten Daten sehen wie folgt aus:

Verwendungskategorie (nach BfR)	**Anstrichstoffe/Dispersionsfarbe**
Expositionsszenario	Malern / große Fläche
Aufnahmepfad(e)	Inhalativ
Häufigkeit	einmalig
Dauer	4 Stunden
Produktmenge pro m²	0,15 kg (laut Internet: www.baulinks.de)

bei 100 m² Fläche	15 kg
Gehalt Lösungsmittel	z.B. 5 %
Raumgröße	30 m³
Raumluftventilation	0,5 L/h
Farbspritzerfläche auf der Haut	840 cm²

Die Firma muss neben der Verwendungskategorie lediglich eine Angabe zum Anteil des Stoffes im Produkt in die Berechnung einfügen. Die Verwendungskategorie ist direkt mit dem Szenario verknüpft. Alle weiteren Werte, die zur Schätzung verwendet werden, werden bei der Beschreibung des Szenarios als Standardangaben formuliert. Weitere Angaben sind nicht erforderlich. Dieses Grundprinzip der Expositionsszenarien kann in REACH für alle Arten von Expositionen und Aufnahmewege formuliert werden.

Als Ergebnis der Schätzung wird bei diesem Beispiel eine Konzentration (inhalative Aufnahme) und ein dermaler Aufnahmewert geliefert, die mit entsprechenden toxikologischen Werten ins Verhältnis gesetzt werden können.

(b) Beispiel aus dem Umweltschutz: Farbmittel für die Lederfärbung

Beispiel: 40 %-ige, wässrige Zubereitung mit Farbmittel für die Lederfärbung

Bildung einer Verwendungskategorie (Nr. 7 der Parameter) in Zusammenspiel aus

- Funktion des Stoffes, hier Farbmittel
- Anwendungsart, hier aufziehen
- Prozesstyp, hier wässriges Bad
- Produkttyp, hier wasserbasierte Zubereitung
- Materialtyp, hier Leder.

Bildung einer Expositionskategorie

Eine zu erarbeitende Leitlinie führt von der Verwendungskategorie zu einem oder mehreren Expositionskategorien, die als standardisierte Expositionsszenarien gedeutet werden. Dafür sind in der Screeningphase (Stufe 1: Generische Expositionsabschätzung) vom Hersteller die folgenden Expositionsdaten erforderlich (siehe Tabelle). Möglicherweise kann das Farbmittel auch für ein anderes Material, z.B. Textil, Verwendung finden. Das würde ein anderes Expositionsszenario bedeuten.

Standard-Expositionsszenario für den Umweltschutz	**Lederverarbeitung**
Lebenszyklusphase	industrielle Anwendung
1. Eintragspfad	Wasserpfad
3. Expositionsdauer	durchschnittlich x Arbeitstage pro Jahr und Betrieb
4. Expositionsort	lokale Emission in lederverarbeitenden Betrieben
5. Stoffeigenschaften	z.B. Wasserlöslichkeit, Dampfdruck, Oktanol/Wasser-Verteilungskoeffizient
6. Stoffmenge	- im Expositionsszenario festgelegte worst case (maximale) Verarbeitungsmenge der Zubereitung pro Jahr und Betrieb - Anteil des Stoffes in der Zubereitung: hier z.B. 40 %

6. Emissionsfaktor	im Expositionsszenario festgelegt: 2 %
8. Expositionserwartungswert	Er wird ermittelt durch eine vorgegebene, transparente und nachvollziehbare Berechnungsformel, in die die Daten der Parameter 1 bis 6 eingehen.
9. Akzeptable Expositionshöhe (Expositionszielgröße)	Sie wird durch den Vergleich des Expositionserwartungswertes mit einem aus Experimenten abgeleiteten Wirkwert für aquatische Lebewesen (akzeptable Expositionshöhe) ermittelt.
10. Emissionsminderungsmaßnahme	- Ausfällung in werkseigener Anlage und Entsorgung als gefährlicher Abfall und/oder - kommunale Kläranlage vor Eintrag in einen Vorfluter

Der Hersteller legt in Kenntnis der Verwendungskategorie fest, welches Expositionsszenario für die Berechnung des Expositionserwartungswertes gewählt werden soll (Stufe 1). Der Stoffanwender überprüft dieses Expositionsszenario. Er kann die Herstellerangaben bei Bedarf durch eigene betriebliche Emissions- und Expositionsdaten sowie Emissionsminderungsmaßnahmen zu den Elementen Nr. 3, 6 und 10 überschreiben (Stufe 2). Eine Expositionsbeurteilung nach Stufe 3 wird nur im Ausnahmefall durchgeführt (bei zu hohen Expositionserwartungswerten nach Stufe 1 und 2) und erfordert aufwändigere Modelle mit ausführlicherem Datensatz.

(c) Beispiel aus dem Arbeitsschutz: Verstreichen von Farbe

Bildung von VEK für das Beispiel: Verstreichen einer Farbe mit 5 % Lösemittel

Parameter zur Kategorienbildung:

Parameter der VEK	**Verstreichen**
2. Aufnahmeweg des Menschen	Inhalativ
3. Expositionsdauer	Täglich, 8 Stunden
5. Stoffeigenschaften	Dampfdruck
6. Stoffmenge	Pro Tag eingesetzte Menge Farbe: kg-Mengen Lösemittel: g-Mengen
7. Art der Tätigkeit/Verwendungsart	Verstreichen, großflächig (offener Umgang)
8. Expositionserwartungswert	Wird durch einfaches Modell aus obigen Angaben ermittelt
9. Akzeptable Expositionshöhe (Expositionszielgröße)	Auf der Grundlage toxikologischer Daten abgeleiteter Wert
10. Schutzmaßnahmen	Raumlüftung (offenes Fenster)
Prozesstemperatur	Raumtemperatur
Aerosolbildung	nein

Auf der Grundlage der hier aufgeführten Parameter kann auf verschiedenen Stufen die Expositionsbeurteilung vorgenommen werden:

1. Stufe:
In einem ersten (konservativen) Schritt wird auf der Grundlage von schematisierten Verwendungsangaben die VEK erstellt und die Expositionsbeurteilung mit einem allgemeinen Modell (z.B. EASE) durchgeführt. In diesem Schritt werden allgemein formulierte Maßnahmen (Lüftung, lokale Absaugung etc.) berücksichtigt. Sind anwendungsbezogene Parameter nicht bekannt (z.B. Expositionsdauer), so werden eher konservative Annahmen gemacht. Der Prozess der Expositionsbeurteilung ist beendet, wenn der Expositionserwartungswert unter der Expositionszielgröße liegt.

2. Stufe:

Ist der Expositionserwartungswert größer als die Expositionszielgröße, so folgt die Expositionsbeurteilung unter Verwendung eines Modell-Szenarios, das weitere Maßnahmen berücksichtigt. Bei unrealistischen Maßnahmen (z.B. geschlossenes System für großflächiges Kleben) müssen die Modell-Szenarien weiter konkretisiert werden (siehe Stufe 3)

3. Stufe:

Berücksichtigung detaillierterer Beschreibungen und verfeinerter Modelle. Dies führt zu realistischeren Annahmen für unbekannte Parameter (z.B. Expositionsdauer). Detailliertere Informationen können ggf. in Branchenlösungen (Branchenprojekte) erarbeitet werden. Hier können auch VSK, LASI-ALMA-Empfehlungen u.ä. zum Einsatz kommen.