Institut für Toxikologie und Umwelthygiene
der Technischen Universität München

Prof. em. Dr. med. Helmut Greim

TECHNISCHE UNIVERSITÄT MÜNCHEN

Hohenbachernstraße 15-17
D-85350 Freising-Weihenstephan
Telefon: 08161/ 71-5600
Telefax: 08161/ 71-5618
E-mail: helmut.greim@lrz.tum.de

Mr. Günther Verheugen
Commissioner of the
European Commission
200, Rue de la Loi

B-1049 Brussels
BELGIUM

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Comments by European Toxicologists to the Discussion about REACH

Dear Commissioner:

On behalf of the undersigning European toxicologists I am sending you a documentation on the ongoing discussion about REACH with specific reference to the use of alternative test systems as a substitute for repeated dose studies in animals.

Sincerely yours,

Prof. Dr. H. Greim

Toxicological Comments to the Discussion About REACH

Summary

It is the ultimate goal of REACH (Registration, Evaluation and Authorization of Chemicals) to identify substances of hazardous properties and to evaluate the risks of human and environmental exposure.
During the last months there has been controversial discussion to what extent in vitro studies and consideration of structure activity relationship provide sufficient information to waive repeated exposure studies. Industry as well as certain regulatory agencies or NGOs support this approach and propose that repeated dose studies may only be required beyond 100 t/a. From a toxicological point of view it has to be stressed that this discussion primarily considers cost reduction and protection of animals, whereas protection of human health and the environment become secondary.

In vitro studies only allow identification of specific hazardous properties, which can be detected by the specific test system. Moreover, appropriate information on the dose response of adverse effects, identification of thresholds and NOELs that are essential for risk characterization cannot be obtained from these studies. Consequently, identification of all relevant hazardous properties and endpoints of adverse effects can only be determined in the intact animal by repeated dose studies such as the 28-days or 90-days studies. In the absence of such information the hazard identification is incomplete and there is no basis for appropriate risk assessment of human exposure. Thus, any waiving of repeated dose studies in animals bears the probability of unforeseen effects in case of acute or continuous human exposure.

From this the undersigning European Toxicologists conclude:

1. **The intention of REACH is to identify hazardous properties in order that a reliable risk assessment can be made and measures taken to deal with chemicals posing a significant risk**
2. **The recent debate has centered on ways in which the well established in vivo methods for risk assessment can be by passed**
3. **The evidence that the available alternatives would support such replacement is weak. Progress to improve their value for risk assessment purposes is bound to be slow because the issues are very complex. As a group of European Toxicologists we strongly support the need for more research support in these areas, but we believe that over claims for progress is damaging their development.**

4. **Under the circumstances two options are available**

    - **To reduce very substantially the estimation of hazard and risk with inevitable adverse consequences for human health and environmental protection**
    - **To continue with the existing methods until such time as properly validated new methods are available**

The attached document stresses these points and clarifies the validity of in vitro data for hazard identification and risk assessment within the framework of REACH. The paper will be further distributed to the member states and the European Parliament. It also will be published in the scientific literature e.g. Archives of Toxicology.

General Comments

From a toxicological point of view the flexibility described in the Annexes (especially Annexes VI - IX) is sufficient to allow waiving of unnecessary tests, in particular animal studies. The Commission's proposal is flexible enough to request further studies if there are substance specific indications for a hazard. A concept to prioritize the need for testing and risk assessment of specific compounds will be developed by the "Agency". Obviously, the currently available information about adverse substance properties and exposure has to be collected at first. Whether additional information is required depends on the quality of the available database.
To identify hazardous properties of chemicals, substance-specific information on the different endpoints is necessary. With increasing information on all relevant endpoints hazardous properties can be identified appropriately. Vice versa, if insufficient information is available no reliable conclusion can be drawn. Consequently, the present concept to define the extent of necessary information by the amount of annual production of a substance is a convention with little toxicological justification.

Information on physico-chemical properties, acute toxicity, local irritation and corrosion, sensitisation and bacterial mutagenicity that is presently required for substances up to 10 t/a (Annex V) only allow hazard identification of these specific endpoints and permit specific labelling or classification. Organ specificity and other very relevant endpoints like fertility, pre- and postnatal toxicity or carcinogenicity are not covered and can only be evaluated by appropriate repeated dose studies in animals. At present, they cannot be extrapolated from information obtained from in vitro tests or QSAR.

It has also to be stressed, that differences in exposure scenarios like private, commercial or industrial may determine the necessary information. Although the size of the exposed population is a relevant parameter for prioritization and risk

management it has to be stressed that from a toxicological point of view these scenarios only differ in intensity and duration of exposure or in the possibility to avoid human exposure in industry or commerce by using personal protection measures or risk reduction measures. The exposure scenarios are therefore important for evaluation of exposure and to prioritize the need for testing and risk assessment but are not suitable to define the extent of toxicological testing.

There is the proposal to differentiate between substances of “high” or “low” exposure to define the amount of testing required. This is without toxicological justification, because the toxic potencies of substances differ widely. High and low exposure can only be defined by the substance-specific threshold or NOAEL of the relevant toxic endpoints and not by exposure. Consequently, "high exposure" describes concentrations or amounts of a substance, which cause adverse toxic effects whereas "low exposure" corresponds to concentrations or amounts without adverse effects. Identification of the potency is described by the NOAEL, which can only be derived from appropriate repeated dose studies (usually a 90-day or at least 28-day study).

In the REACH system a step-wise registration is intended. The registration deadlines are 3 years for substances >1000 t (Annex VIII) and for substances with carcinogenic, mutagenic properties and those toxic for reproduction (CMR); 6 years for substances 100 - 1000 t (Annex VII), and 11 years for substances 10 - 100 t (Annex VI) and 1 - 10 t (Annex V). There are alternative proposals for a prioritization of the registration of substances based on their risk for man and environment. However, to get knowledge about the risk of a substance for man and environment, appropriate data on exposure (man and environment) and on the intrinsic hazard of a substance are needed. As experience shows, it is very problematic to gain reliable data on exposure. On the other hand, available datasets on the toxicological (or ecotoxicological) endpoints may differ substantially. For such a prioritisation only the available data could be used and might not allow proper hazard identification in many cases.

Substances produced and imported in quantities from 1 to 10 tonnes per year (Annex V)

For substances referring to Annex V, toxicological data on skin and eye irritation in vitro, skin sensitisation and bacterial mutagenicity are required.
Under specific conditions, the tests on skin and eye irritation and on skin sensitisation do not need to be conducted; e.g.:

- If substances are corrosive, strong acids or bases, or flammable in air at room temperature;
- If other tests already performed indicate no necessity of the test to be performed;
- If other tests already performed are adequate to classify a substance.

In the case of positive results of the bacterial mutagenicity test, further mutagenicity studies shall be considered.

The information, which has to be supplied for substances referring to Annex V, is very limited and only permits the evaluation of local irritation and corrosion, skin sensitisation and bacterial mutagenicity. Substance-specific systemic effects on organ systems including reproduction and cumulative effects or effects of metabolites will not be covered. The information requested in Annex V does therefore not permit risk characterisation unless additional data from repeated dose studies are available. The situations, under which a waiving of the studies on local irritation and sensitisation is possible, are supported.

Some Member States have called for a risk-dependent testing programme for substances between 1 and 10 tonnes because the information required so far has been criticised as too costly. Customised testing programmes based on the available data should be established for each individual substance instead. Collection of currently available information has to be supported. However, if the available information does not exceed the small amount of data required in Annex V assessment of the potential risk of a substance is not possible unless data on exposure as well as on systemic effects and their dose response are available, which can only be obtained from repeated dose studies in animals.

Substances produced and imported in quantities from 10 to 100 tonnes per year (Annex VI)

For substances referring to Annex VI, the toxicological data of Annex V have to be supplied. In addition, further data on skin and eye irritation in vivo (if the data from Annex V are not adequate for classification), data on genotoxicity in vitro in mammalian cells, acute toxicity, repeated dose toxicity (28 days), reproductive toxicity (a screening test for reproductive/developmental toxicity and a developmental toxicity study) and a toxicokinetic assessment of available information are required. In Annex VI possibilities are given not to perform the tests required:

- Test on **eye and skin irritation** may be waived if substances are corrosive, strong acids or bases, or flammable in air at room temperature
- The **in vitro genotoxicity** tests in mammalian cells do not have to be performed if adequate data from in vivo studies are available or if the substance is a known carcinogen category 1 or 2.
- The studies on **acute toxicity** may be waived if precise doses of the substance cannot be administered due to the chemical or physical properties of the substance or the substance is corrosive or flammable in air at room temperature.
- The **28-day toxicity study** does not need to be conducted if a reliable sub-chronic or chronic study is available or the substance undergoes immediate disintegration and there are sufficient data on the cleavage products or **relevant human exposure can be excluded**.

- The studies on **reproductive toxicity** may be waived if the substance is a known genotoxic carcinogen or a germ cell mutagen and appropriate risk management measures are implemented or if **relevant human exposure can be excluded**.

Under specific exposure and hazard conditions, further tests (sub-chronic toxicity study, two-generation reproduction toxicity study) have to be performed.

The information required in Annexes V and VI for substances produced or imported in quantities of 10 to 100 tonnes per year gives a basic data-set which allows a first evaluation of the toxicity of the substance. If hazardous properties are detected, the Commission's proposal seems to be flexible enough to ask for further data. The possibilities listed under which data may not be supplied are supported. However, up to now, there is no definition for "relevant human exposure can be excluded". This includes the situation with no human exposure at all. From a toxicological point of view this may also include exposure to low concentrations of a substance which does not elicit adverse effects. However, in the absence of adequate data from a repeated dose study, derivation of a NOEL for adverse effects is not possible.

To further reduce the costs of testing there is discussion to request the 28-day toxicity studies in particularly well-founded individual cases only. The 28 days repeated dose toxicity study or a similar study with repeated exposure is the minimal requirement to evaluate the organ specific effects of a compound, the dose response and the toxic potency of a substance. If this study is not available, evaluation of systemic effects of the substance is not possible. Also, it is not possible to decide, whether further testing (e.g. long-term toxicity, reproductive toxicity or carcinogenicity) may be necessary. Therefore, an appropriate repeated dose toxicity study is generally required as mentioned in Annex VI. Waiving of this test, especially under the condition "relevant human exposure can be excluded" has to be evaluated extremely carefully. The reason for this exposure-based waiving has to be substantiated case by case.

Under the condition "relevant human exposure can be excluded" waiving of the tests on reproductive toxicity (a screening test for reproductive/developmental toxicity and a developmental toxicity study) is also possible in Annex VI. If these data are not available, no conclusion can be drawn on reproduction and on prenatal toxicity. Especially, in the case of prenatal developmental toxicity, even a single exposure can induce prenatal toxic or even teratogenic effects. If exposure-based waiving of this test is discussed, the exposure situation has again to be evaluated extremely carefully.

Substances produced and imported in quantities of over 100 tonnes per year (Annexes VII and VIII)

For substances referring to Annex VII, the toxicological data of Annex V and VI have to be supplied. In addition to the 28-day toxicity study, a 90-day sub-chronic toxicity study and studies on reproductive toxicity (a developmental toxicity study and a two-generation redroductive study) are necessary unless they are already provided as part of Annex VI requirements.
In Annex VII possibilities for waiving of these tests are given.

- The **90-day toxicity study** does not need to be conducted if a reliable short-term toxicity study (28 days) is available showing severe toxicity effects according to the criteria for classifying the substance as R48, for which the observed NOAEL-28 days, with the application of an appropriate uncertainty factor, allows the extrapolation towards the NOAEL-90 days for the same route of exposure; or a reliable chronic toxicity study is available; or the substance is non-reactive, insoluble and not inhalable and there is no evidence of absorption and no evidence of toxicity in a 28-day “limit test”, particularly if such a pattern is coupled with limited human exposure.
- The **tests on reproductive toxicity** may be waived if the substance is a known genotoxic carcinogen or a germ cell mutagen and appropriate risk management measures are implemented.

Under specific exposure and hazard conditions, further studies have to be performed.
For substances referring to Annex VIII, the toxicological data of Annex V, VI and VII have to be supplied. In addition, a long-term repeated toxicity study (≥ 12 months), a carcinogenicity study or other studies might be proposed.
In Annex VIII possibilities are given not to perform the studies required:

- The **two-generation reproduction toxicity study** may be waived if the substance is a known geotaxis carcinogen or a germ cell mutagen and appropriate risk management measures are implemented or the substance is of low toxicological activity, it can be proven from toxic kinetic data that no systemic absorption occurs via relevant routes of exposure and there is no or no significant human exposure.

The testing requirements established in Annexes VII and VIII can be considered sufficient to identify the relevant toxic endpoints. Starting from a basic toxicological data-set performance of further studies will be decided by a substance-tailored testing strategy. This also includes evaluation of specific exposure scenarios. Exposure-based waiving ("no or no significant human exposure") is mentioned in Annex VIII for the two-generation reproduction toxicity study.

Conclusion

It is the ultimate goal of REACH to identify substances of hazardous properties and to evaluate the risks of human and environmental exposure. In vitro studies allow identification of hazardous properties of substances, but only those which can be detected by the specific test system. Even when the test system has a metabolic capacity its appropriateness must be verified in the intact organisms. Consequently, identification of all relevant endpoints of adverse effects, their dose response, thresholds and NOELs can only be determined in the intact animal by repeated dose studies such as the 28 days or 90 days studies, the latter being more sensitive and covering more endpoints than the former. In the absence of such information the hazard identification is incomplete and without information of the dose response obtained from these studies there is no basis for appropriate risk assessment of human exposure. Thus, the concept that the number of endpoints to be explored is dependent only from the amount produced of a chemical bears the probability of unforeseen effects in case of acute or continuous human exposure.

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Prof. M. Arand, Institute of Pharmacology and Toxicology, University of Zurich, Switzerland
Prof. Herman Autrup, Department of Environmental and Occupational Medicine, University of Aarhus, Denmark
Prof. Hermann M. Bolt, Institute of Occupational Physiology, University of Dortmund, Germany, Vice chair, Scientific Committee of Occupational Exposure Limits, DG Employment and Social Affairs
Prof. James Bridges, University of Surrey, United Kingdom, Chair, Scientific Committee on Emerging and Newly-Identified Health Risks, DG Health and Consumer Protection
Prof. Erik Dybing, Norwegian Institute of Public Health, Division of Environmental Medicine, Oslo, Norway
Prof. Rémi Glomot, Paris, France, Past-President of the French Society of Toxicology, Past-Vice-President of the International Union of Toxicology
Prof. Helmut Greim, Institute of Toxicology and Environmental Hygiene, Technical University of Munich, Germany, Chair Scientific Committee on Health and Environmental Risks, DG Health and Consumer Protection
Prof. Vito Foa, Institute of University of Milan, Italy, Chair Scientific Committee of Occupational Exposure Limits, DG Employment and Social Affairs
Prof. Rolf. Schulte-Herrmann, Institute of Cancer Research, Medical University of Vienna, Austria