Position paper of the German Society of Toxicology on the EU Chemicals Strategy for Sustainability

Currently the European Commission is pursuing a new "Chemicals Strategy for Sustainability" (COM(2020) 667 final). This strategy is part of the European 'Green Deal' and is a central building block towards a so-called 'Zero Pollution' environment ('Towards a Toxic-Free Environment'). The strategy aims at increasing the protection of human health and the environment from hazardous chemicals and at the same time promoting innovative solutions for developing safe and sustainable chemicals. The strategy lists more than 80 individual regulatory actions that are planned to be implemented in parallel legislative processes over the coming years. The proposed regulatory actions concern a whole range of EU regulations such as the European Regulation on Registration, Evaluation, Authorisation and Restriction of Chemicals (REACh), the Regulation on Classification, Labelling and Packaging of Substances and Mixtures (CLP Regulation), as well as numerous specific regulations on toys, cosmetics, plant protection or biocides.

The German Society of Toxicology in principle supports the European chemicals strategy for sustainability and therefore welcomes the efforts to further increase the protection of human health and the environment from hazardous chemicals and to promote innovations for the development of sustainable chemicals.

However, some of the planned far-reaching regulative actions are worth discussion from the perspective of human toxicology. In accordance with the mission of the German Society of Toxicology, this paper does not deal with matters concerning ecotoxicology.

The new chemicals strategy concerns inter alia, certain substances with endocrine effects, so-called endocrine disruptors, as well as combination effects of chemicals.

Endocrine disrupting chemicals

Endocrine active chemicals act similarly to endogenous hormones, they are able to inhibit the action of endogenous hormones or to alter circulating hormone concentrations in the organism. This property (endocrine activity) may be based on a number of very different mechanisms. If the mechanisms are leading to adverse effects (e.g. disturbances of the thyroid function with the consequence of cardiac arrhythmias), these substances are called endocrine damaging substances or endocrine disruptors. The World Health Organisation (WHO) defines endocrine disruptors restrictively as exogenous substances or mixtures that alter function(s) of the endocrine system and consequently cause adverse health effects (IPCS/WHO 2002).

The current legal requirements of the standard experimental tests for chemicals, plant protection products and biocides in combination with the regulatory registration and authorisation procedures ensure that harmful effects on human health are detected. Risk assessment in the authorisation procedure for plant protection products and biocides allows quantifying the risks of existing exposures. Appropriate regulatory follow-up may be chosen, such as restrictions on the manufacture, placing on the

market or use of a substance, to ensure that endocrine disruptors can be managed safely and that no adverse health effects may occur in workers and the general population.

The planned new Chemicals Strategy amendments envisage that the system of classification and labelling of health hazards of substances (CLP Regulation) shall be extended to include a separate hazard class for endocrine disruptors. In doing so, a specific mechanism of action causing an adverse effect would lead to a separate additional classification. This planned procedure is based on the assumption that endocrine disruptors are a particularly critical group of substances which need to be regulated more stringently. However, existing legislation already provides a good basis for effectively assessing the health effects of endocrine disruptors. Substances that cause adverse effects via an endocrine effect are currently classified as toxic to target organ(s), reproductive toxicants or carcinogens if respective data are available as are substances with non-endocrine mechanisms of action that cause such effects. The assessment on the basis of observed adverse effects has proven to be effective and is also in line with the system of hazard classification of substances that act via other molecular mechanisms. A separate classification based on specific molecular mechanisms of action, on the other hand, would consequently also have to be established for other mechanisms that lead to adverse effects. With the resulting double classification, however, the system of classification and labelling would fail to achieve one of its most important goals, namely to provide targeted information to those who are exposed to these substances to protect them from possible harm specifically addressed on the label.

Additional safety factor for combination effects

Humans and the environment are simultaneously exposed to a large number of chemicals. Up to now, combination effects of chemicals have been taken into account only under specific circumstances. The EU proposal is to cover combination effects on a regular basis using an additional general default assessment factor. The underlying assumption made by the EU is that the effects of chemicals generally add up during combined exposure. Therefore, all guidance/limit values derived under REACh, such as the 'Derived No-Effect Level' (DNEL) values, which are set for individual substances, shall be reduced by a certain standard factor because of general potential co-exposure to other chemicals.

The EU approach that effects of substances in mixtures add up is only applicable under certain premises. An interaction or combination effect of substances is likely if they trigger an effect via the same initiating mechanism of action or intervene at different points in an adverse outcome pathway. Even if in cases of different toxicological mechanisms of action the occurrence of an additive combination effect of chemicals cannot fully be ruled out, it is mechanistically improbable. Moreover, combination effects are generally only to be expected when people are exposed to jointly acting substances in higher doses exceeding the health-based guidance values (e. g. ADI, TDI, DNEL) established for the individual substances sharing the same mode of action. In these cases, a combination-specific additional safety factor could be determined in a targeted approach from the dose-response data of the individual substances.

The regulation of phthalates is an example how under the existing chemicals legislation verified combination effects have been taken into account by applying specific regulative measures. From a scientific point of view, it would be premature and without scientifically sound basis to lower all health-

based guidance or limit values through the introduction of a standard default factor in addition to the existing safety factors. It has to be noted that research projects funded by the EU and its member states are ongoing aiming to expand the state of knowledge in this field, and to improve the knowledge basis for future decisions.

At the moment, a "blanket" consideration of combination effects would abandon the proven path of a risk-based toxicological assessment of chemicals.

Concluding remarks

In recent decades European environmental and chemicals legislation was instrumental for achieving improved health and environmental protection. The German Society of Toxicology explicitly supports the aim to further increase this very high level of protection. In doing so, it is crucial (i) setting adequate priorities taking into account limited resources, (ii) establishing measures and procedures which are scientifically justified and transparent, and (iii) including the existing state of scientific and toxicological knowledge in strategic planning. In this way any amendment of chemicals legislation brought forward should first focus on streamlining and more efficiently implementing existing options to ensure health protection. An example would be an improved availability of experimental test data on the toxicity of substances. Long-term studies should be demanded as a matter of principle in the case of toxicological indications of a carcinogenic effect for highly market-relevant substances, which, unfortunately, is currently only an option under REACh. Furthermore, it would be advisable to adapt the OECD test guidelines for chemicals more quickly to the current scientific knowledge.

The changes in chemicals legislation discussed here and proposed by the EU Commission would lead to an even stronger emphasis on the intrinsic hazard properties of substances as regulative basis at the expenses of a toxicological health risk assessment, established and successfully working worldwide for decades. Potentially far-reaching regulatory consequences, would result, some of which would not make sense from a scientific point of view.

Position paper of the Advisory Committee of the German Society of Toxicology for the German Society of Toxicology

The Advisory Committee of the German Society of Toxicology (AC) is elected by the members of the German Society of Toxicology and consists of representatives from academia, industry and administration to guarantee a broad range of toxicological competence. The AC presents and justifies its activities to the members of the German Society of Toxicology, for example at the yearly plenary meeting. The German Society of Toxicology is the largest scientific toxicological organization in Europe, with more than 1300 members.

References for further reading

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