Executive summary

Every day, people are exposed to all kinds of substances, through swallowing and inhalation among other things. In this advisory report, a Committee of the Health Council of the Netherlands considers the possible adverse health effects of this type of combined exposure.

The Committee first sketches a methodological framework for determining the harmfulness (toxicity) of random combinations of substances, in aid of risk assessment. Risk assessment is intended to determine the nature and size of (potential) health impairment. This advisory report describes how the risk assessment for combinations of substances relates to that for separate substances. The framework the Committee outlines provides a starting point when ascertaining the number of recommended exposure limits that allow the consequences of exposure to be determined. It also helps in the derivation of recommended exposure limits and working with them. The Committee also assesses the degree to which research results can be applied to the circumstances under which combined exposure actually occurs, and the consequences for the way in which recommended exposure limits are derived and applied. Finally, the Committee presents a method for ranking combinations according to the severity of the health impairment.

The Committee discussed its ideas at a working conference with an international group of specialists in the field. The insights obtained at this conference have been incorporated into this advisory report.

Combined effect

The methods for expressing combined effect in figures have not essentially changed since 1985, when the Health Council's first advisory report examining the problem of exposure to combinations of substances was published. However, it is now possible to express the combined effect in figures for more substances. The Committee presents a proposal for a structured approach to combination issues and links it to the 1985 advisory report's classification system based on biological criteria and adapted to current scientific knowledge. This system, which examines substances in pairs, amounts to the categorization of the combined effect into four types, on the basis of the working mechanism. It is based on whether or not the toxic effects correspond and whether or not interaction occurs. Calculation rules exist for the similar and dissimilar effects without interaction, known as dose and response addition. These rules can be used to derive the effect of the combination from the effects of the separate substances and make it possible to determine the degree to which the recommended exposure limits for separate substances provide protection. There is no universal rule for the similar and dissimilar effects in the case of interaction. The system's successful application depends on clarification of the working mechanism. Although this knowledge is available for an increasing number of substances, its collection in routine toxicological studies of substances does not take place as a matter of course. The Committee calls for an improvement in this situation, in line with its recently published advisory report on taking a more efficient approach to research into the health risks of substances. Given the quantification problems, the Committee also recommends arranging for research to be conducted with a view to establishing a well-founded relationship between the nature of the combined effect and the type of calculation rule. This could remove the existing knowledge gap in this field.

The framework presented by the Committee is not a detailed protocol but leaves the interpretation of data in specific situations to specialists. It can be seen as an attempt to give a structure to risk assessment for combinations of substances.

Combinations

For practical reasons, the Committee distinguishes between mixtures and specified (or defined) combinations of substances. A characteristic of mixtures is that the exposure to the components occurs simultaneously and via the same route(s). Information about the composition of mixtures varies. For example, many details are known about the composition of paint fumes whereas only limited data is available on polluted air. The term 'specified combination' means that all substances are known, regardless of whether they occur together. In the case of a specified combination different exposure routes may exist and the exposures may be independent of one another. An example is the combination benzene and dioxin: exposure through inhalation and food respectively. Although some combinations fit into both categories, it is useful to distinguish between mixtures and specified combinations for the risk assessment. Different approaches are generally considered for the two types in the risk assessment. The best approach in a given case depends on the available data on composition and toxicity.

Substance combinations can be treated as a single entity or as if composed of fractions or separate constituents. In this context 'fraction' refers to a group of substances with similar physico-chemical properties. The different methods are shown alongside each other in a flow chart. The Committee recommends going through the entire chart and, rather than making a choice in advance, only making it once the assessment indicates the most suitable approach. To enable the best choice, it is important to examine all of the information together. If required data on one or more methods is incomplete or missing, fewer possibilities will obviously be available. Theoretically, the aforementioned approach can be taken for any combination and for any toxic effect. Determining for the end result is the knowledge available on the nature and toxicity of the substances concerned.

In principle, all three approaches are appropriate for risk assessment. Experience should show how reliable they are. The Committee calls for the component-based method to be tested with combinations of increasing complexity. This will make it possible to determine whether it is scientifically sound and practical.

Interpretation of toxicity data

One of the most difficult parts of assessing the consequences of combined exposure is estimating the magnitude of the combined effect for specified substances under real-life exposure conditions. For example, the combined effect of realistic concentrations in the air generally has to be derived from observations on (much) higher concentrations. Since 1985, more empirical data has been gathered about the consequences of exposure to such 'low' concentrations of substances in combination. The scarce findings are in line with the recommended calculation rules and the Committee believes they do not give grounds for assuming that commonly used recommended exposure limits provide insufficient protection. The Committee therefore sees no reason for changing the derivation of recommended exposure limits and the way the numbers are dealt with in the risk assessment of combinations. However, the scope of the research was limited. Moreover, the analyses concerned short-term exposure to a small number of substances. Therefore, the Committee believes additional research is necessary.

Setting priorities

The Committee also presents a prioritization method for risk assessment. This enables situations involving combined exposure to be systematically compared and ranked according to how problematical they are.

The hazard quotient for each substance in the combination is determined by dividing the actual exposure by an exposure limit. The quotients are then combined to produce a hazard index. In the case of a similar effect, this is done by adding the quotients. In the case of a dissimilar effect, the highest quotient is chosen. The level of risk increases as the resulting number increases.

The hazard index does not take into account the possibility of interaction. Taking this into account refines the index. Up to now, this refinement – correction with weight-of-evidence scores – has only been worked out for similar actions. For each pair of substances the data that (may) indicate interaction is divided into categories and this information is qualitatively weighed according to evidential value. Then, all possible interactions are placed in a matrix, together with the alphanumerical weight-of-evidence. In this matrix each cell relates to a pair of substances. Subsequently, the qualitative weight factors are replaced with numbers and the cells are weighed together. At this stage, the actual exposure is also taken into account. The reason for concern increases in proportion to the final result.

The method can be used for all kinds of combination issues. The variant that is most suitable depends on the purpose and the required accuracy. However, increasing accuracy also means increasing the laboriousness of the procedure. Practice should determine the feasibility of the method in its various forms. Further validation is necessary, as is a sensitivity analysis.