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Direktor:
Professor Dr. Carl Friedrich Gethmann

Environmental Standards.

Combined Exposures and their Effects
on Human Beings and their Environment

– Summary –

by

Christian Streffer et al.

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Graue Reihe Nr. 19

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Postfach 14 60, D-53459 Bad Neuenahr-Ahrweiler
Telefon: ++49 - (0)2641 - 973 - 300, Telefax -320
e-mail: europaeische.akademie@dlr.de

Director:

Professor Dr. Carl Friedrich Gethmann (V.i.S.d.P.)

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Introduction

Increasing technicalisation and population density have led to the situation where mankind and its environment are exposed to a multitude of factors of which very often only little is known about their mid- and long-term health consequences. The development, operation and disposal of technical equipment and products release harmful substances and physical agents like ionising radiation and noise that could have an undesired effect on mankind and its environment. Such side effects of technical development and the intensified public discussion about such topics have contributed to the fact that a mainly unreflective, optimistic view about progress, like the popular belief in the 1950s and 1960s, can hardly be upheld nowadays. Instead, far more often the pendulum swings in the opposite direction, most apparent in the demands for a “zero exposure”. One of the means to pave a future and acceptable way amongst such extreme views is the creation and use of environmental standards.

The knowledge about harmful effects of diverse individual exposures on the environment and human health has resulted in the definition of environmental standards for individual chemical and physical agents. This individual substance orientated procedure is in accordance with the fundamental medical research analysis of contextual responses, which concentrates mainly on individual exposures. The examination of combined lowest dose exposures, which correspond much more realistically to exposure conditions in the actual environment than the analysis of single substances, entails major methodological difficulties in the experimentation and evaluation procedure. However, the potential risk of combined exposures and public discussion thereof make the analysis of this topic area a desideratum of the utmost priority.

From a scientific, medical, sociological, economic, legal and philosophical perspective, this study will examine the necessity, realisability and consequences of *environment standards for combined exposures*. The main focus will concentrate on human exposure, especially to carcinogens and genotoxicological effects, and on the exposure of a certain selection of plants, which will serve to answer the most pragmatically urgent questions.

Taking account of the effect mechanisms involved a categorisation of combined exposures will be made, on the basis of which criteria will be established, which, regardless of the complexity of the context of exposition, will enable us to set limit values in order to maintain or achieve concrete environment quality standards. The study shall help to recognise and reveal knowledge gaps and possible solutions. The results of this project shall also form the basis for improving the evaluation of combined exposures, in order to enable the creation of an efficient framework for the relevant legal regulations and economic procedures.

Methodological Foundations

Environmental standards or limit values are understood as the concrete, quantitative expression of environmental quality targets. They are the means to their realisation. Environmental quality targets in their turn represent normative concepts with regard to the quality of man's environment or that of other life forms. In some respects, environmental quality targets are, in condensed terms, the guiding concepts of environmental policy, expressing general environment(s) goals in such areas as health, sustainability and system functionality etc.

Environmental standards do not represent a natural but a cultural phenomenon, i.e. conventional settings. In the first instance they are prescriptive and not descriptive objects. However, natural phenomena play a "decisive" role in the determination of environmental standards. The inter-relationship between the observation of nature and the regulatory stipulation of procedures can be illustrated by differentiating between "threshold value" and "limit value". Threshold values are indeed natural phenomena that can be shown on a graph as curve peculiarities ("thresholds"). A threshold value represents a certain relationship between a cause – i.e. the exposure – and its effect. It is a measured value that indicates, for example, a dose or dose range upon which a certain effect occurs or does not occur. In contrast to this, the *limit value* indicates at which point in the cause-effect relationship a course of action (also including the use of a device, apparatus or large-scale industrial plant) shall have its "limit".

Finally an *environmental quality target* stipulates what shape or form a certain sector of the environment *shall* or *shall not* have. In order to achieve such a target, the limit will be determined by a limit value, the observance of which being the (assumed) minimum prerequisite that has to be fulfilled in order to achieve this target.

Threshold values, i.e. the corresponding threshold range, are determined in scientific experiments and can be displayed on a graph as curve properties. However, it is by no means possible to give threshold values for every kind of effect. In contrast, limit values are set according to certain aims. They may possibly correspond to or be orientated to threshold values. But even the use of safety margins, for example, already leads to a difference between threshold value and limit value. By the very fact that stochastic values are characterised by the lack of a threshold, they represent a twofold problem. Firstly because of the effect even at the lowest dose and secondly due to the lack of a threshold for setting a limit value within a dose-response diagram. Therefore, different characteristic points have to be found. When measuring the risk acceptability of stochastic effects, it is possible to orient to the mean bandwidth of the background exposure, assuming there is pragmatic "normative" indifference to this.

In analysing combined effects, the terminology used is of particular importance. There is no standard terminology to be found in the relevant literature on this subject. Indeed, one may speak of a "confusion of terms". Therefore, one of the aims of this study is by way of formulation to create a standard terminology to facilitate and enable communication within and between the individual disciplines concerned.

A *phenomenological terminology* of combined effects in a case when several substances also individually applied are combined could look as follows:

Example of two substances A and B (x = A or x = B)

$E_{A+B} > E_X$	synergism relating to x	S (A,B) or S(B,A) resp.
$E_{A+B} < E_X$	antagonism relating to x	A(A,B) or A(B,A) resp.

Synergism and antagonism have to be qualified i.e. a reference substance x has to be indicated. The choice of a reference substance however may not be interpreted in a mechanistic fashion, e.g. that an antagonism in relation to x would mean that the other substance or substances would have an effect on x. Effect in a chemical context has to be determined as a symmetrical relationship. In addition, it must be taken into account that a synergism and antagonism of two substances do not have to be effective over the entire range of concentration. If a reference substance is not explicitly indicated, the substance that singularly shows the strongest effect will be taken as a reference point.

To extend the phenomenological terminology, additivity models may be used as comparative tools. However, the description of the deviations from such models have to be clearly differentiated from a terminological point of view from the phenomenological terminology.

The starting point for the formulation of the dose-additivity model are equal increments in the dose-response relationship of individual substances. It is assumed that the doses of single substances, possibly provided with a constant factor, can be added up in order to determine the effect of a combined dose on the basis of a common dose-response relationship. The effect of one substance will thus be equated with that of the other component of the mixture, or as a dilution of same. In practice, the sum of the individual doses is calculated and the effect is read from the common dose-effect curve on the graph. In the effect additivity model, single effects are simply added together to determine the combined effect. The effect additivity model can therefore be applied to any combinations of the same effect.

The model involving independent or relative effect additivity is based on the assumption that the combined effect of single doses is the result of a fictitiously assumed consecutive exposure and that the individual effects are related to the overall effect, in such a way that the effects of the individual doses relative to one another each correspond to a part of the overall effect (actual effect subtracted from overall effect).

The possible consequences of choosing a model in the order of zero approximation can be illustrated using the example of doses comprising combined substances, which when administered alone show no effect. Assuming effect additivity involving a combination of any given number of substances the concentrations of which individually show no effect also shows no effect. However, if one assumes dose additivity, the sum of individually ineffective doses may well result in a relative dose which is effective. At present environmental law often applies the "more cautious" dose additivity model subject to more precise scientific results.

Limit values, as boundaries for political decision making, require legitimation, therefore the rational criteria for defining limit values has to be discussed. Especially important is the question as to how rational it is to set limit values which are not, or not directly, based upon threshold values. To justify limit values, environmental quality targets play an important role. In the interest of a democratically acceptable environmental policy it has to be demanded that the determination of environmental quality targets and the setting up of corresponding limit values is accomplished in a rational manner.

The rationality of an action is measured against its desired ends. Environmental standards have to fulfil the role of protecting man and nature from harm, i.e. when envisaging potentially harmful action to stipulate risk limits. Hence the key term risk is latently at the core of the discussion on environment standards. When it is a matter of rationality in determining environmental standards and the establishment of limit values, it is important to address the question as to whether and, as the case may be, in what way it is possible to weigh the risks rationally.

When setting limit values not only shall certain risks be excluded but also certain risks are often tolerated or accepted. Therefore all risk comparisons, which are the core element for setting limit values, contain a normative element, in so far as a limit value implies that anyone, who is subject to this limit value, may have to tolerate certain harmful consequences and may be permitted to subject others to the same consequences, i.e. such that correspond to a lower degree of risk than that stipulated in the limit value concerned. However, current political discussion makes it abundantly clear that such tolerant behaviour is in no way always readily taken for granted. The normative problem can therefore be boiled down to the question as to which risks can be accepted at all and by what right. The cause of controversial discussions in this context lies in the differing evaluation of commensurateness and risk acceptability.

The question of what others can be expected to accept has always been a fundamental problem in society. However, at the moment, in the context of establishing limit values, this is an even more controversial topic. Firstly, it must be remembered that the question of de facto acceptance fundamentally does not provide any reliable criteria for establishing a legitimate set of limit values. De facto acceptance is as a rule in content vague and over a longer period of time unstable. The particular interests of individuals and groups often lead to diverging expectations. However limit values should principally be acceptable to anyone and be of long-term validity. Therefore, they have to be the instrumental result of mutual objectives. To resolve disagreement with regard to set purposes it is necessary to reach understanding regarding the pursued ends, which in many cases may be realised through various, different purposes. However, discursive conflict solving may be easier, if common objectives are already explicitly or implicitly shared. Conclusions can therefore be drawn from discovering which purposes and objectives actors in society, by virtue of their own actions, implicitly already accept ("revealed preferences"). On the basis of such a set of purposes an actor can be required to accept that a certain degree of risk may be involved in a given action if he otherwise accepts risk on basis of the same subjective benefit/harm assessment (principle of pragmatic consistence). Such a rule would constitute a criterion for risk acceptability.

The principle of pragmatic consistency therefore assumes that from the actions of the agents it is possible to infer their willingness to accept risks. This process can be reconstructed as a fictitious discourse. In this a statement can be incorporated, which, though never actually expressed, still represents an "eloquent testimony".

Not acceptance but acceptability is therefore the criterion for justifying valid demands expressed in the form of environmental standards. The question of acceptability therefore raises the problem of justifying norms, i.e. universal requirements (requirements applying to everybody). Justification problems of this kind are the topic of the philosophical discipline Ethics, while the factually propagated or executed imperatives make up elements of morals currently in force.

In order to be of purpose, environmental standards have to relate to proven effects or at least scientifically plausible effect estimates. In principle one has to accept a broad mechanism, consisting of a chain of steps along the path to the final effect. In addition, effects cannot always be defined as isolated effects, e.g. phenomenal health damage. Even the accumulation in the human body of a certain chemical which in itself is not harmful, may produce a damaging effect. Thus certain substances having accumulated in the body's fatty tissue may find their way into breast milk and have a harmful effect on the infant. In this context it also becomes clear that to ascertain effects and causes implies considerable requirements with regard to the measurability of dependencies. Only when exposure to a harmful substance is accessible to experimental analysis and only when the effect can be observed, can one speak of cause and effect in a *meaningful* way.

In the environmental legislation in Germany and other European countries there is no valid, uniform conception of how to set up environmental standards. On the contrary, current environmental legislation is guided by a variety of very different principles. Thus, the principle of protection, the precautionary principle with its large array of various derived principles, the principle of minimising total cost, the principle of cost-effectiveness or the principle of sustainability are applied.

This kind of plurality of principles is unsatisfactory for methodological reasons. Simple examples will help to explain that the different principles will lead to different results. This applies for example to the alternative use of the precautionary principle and cost effectiveness.

For every principle, however, areas can be cited in which application is plausible. The principle of precaution for example is meaningful if one assumes harmfulness on the basis of scientific criteria, and when little is known about the extent of cause and effect.

To the same extent as knowledge grows about the quantitative relationships the more the application of the principle of precaution loses its plausibility, since the growing level of knowledge achieved enables more precisely targeted procedures.

Precise knowledge about the quantitative relationships may under certain circumstances allow preventive measures to be entirely abandoned in favour of aftercare procedures (e.g. repair of material damage). Finally one should not lose sight of the fact that it is nonsensical from a pragmatic point of view and legally not permissible in view of the principle of proportionality to undertake extensive precautionary measures against extremely small risks. If sufficient knowledge is available, targeted measures can be undertaken under consideration of the relevant risks.

Considerations with the objective of choosing an environmental policy principle within fundamental, environmental policy framework conditions, such as the quality of existing knowledge or the type of risks involved, provide a selection criterion, which will permit a selection commensurate to each context. As a meta-principle we shall call this the *weighing principle*. The application of individual environmental policy principles will be decided upon in accordance with this weighing principle. Depending on the scope of the relevant knowledge, the weighing principle will also help to derive the most urgent research imperatives.

The principles of trans-subjectivity and consistency are subsidiary to the weighing principle, since the result of weighing should be dependent on consistent conditions and not on the weighing person or context by whom or in which the weighing is conducted.

Scientific Foundations

Dose-Response Curves and Models

The biological effects of chemical substances and physical factors can be represented by dose-response curves, which are very valuable for the analysis and evaluation of toxic effects of agents, singly or combined and in the context of environmental standards especially in the lower dose range.

For certain effect mechanisms it is possible to develop mathematical dose-response relationship models for reversible and also for irreversible effects. However, the extrapolation of the medium and high dose range into the environmentally relevant lower or lowest dose range is unsatisfactory, since there is either no or very little available experimental data in this area. The application of a model to sparse data points within the lower dose range is also hampered by the fact that the differences, for example, between sigmoid and exponential curves are very small.

An analysis of numerous experimental and epidemiological data in this lower dose range revealed an almost identical shape for sigmoid and polynome function curves with a linear or linear-quadratic equation, which is an interesting fact for environmental standards and makes it desirable to further analyse the applicability of sigmoid curves in this context. The analyses and comparisons showed that mutagenic effects or tumour frequencies could also be well represented by sigmoid curves.

Given the combined effect of two or more agents, it is possible that stronger or even weaker effects can occur than in the case of effects of a single agent, whereby possible effects within the lower dose range are especially interesting with regard to environmental standards, which, for example, occur frequently if the agents reveal unidirectional toxic effects. However, numerically those combined effects prevail in which different agents show different biological effects, in as far as these have a biological effect at all. In such cases one should not expect any combined effects or interactions. On the contrary one should expect a parallel or consecutive sequence of different effects.

Combined effects can on the one hand be compared either with the corresponding effect of the single agents or with the pharmaco-/toxicodynamic models of combined effects. Due to the differing terminology (“additive”, “synergism“), test approaches (e.g. fixed dose or mixture experiments), and the various types of graphical presentation (e.g. dose-response curve or isobolograms), it is a difficult task for the non-expert to find his way in this field. With regard to environmental standards for the combined effect of agents, the mixed approach and the analysis of dose-response curves appear to be the most expressive. In this procedure the curves of the components will be created either in a single or mixed application (with a fixed dose ratio) and the “mixture curves” can be compared with theoretical combined effects.

The dose-additivity and independent model, which can be based on certain mechanisms, are of special interest for the present study. In the dose-additivity model each agent in the combination reacts as a dilution of one particular substance. In the case of independence the agents act according to different mechanisms but lead to the same (toxic) effect independently. The mathematical effect-additivity model calculates combined effects that equal the sum of all single effects. Differences or similarities in the combined effects of these models explain themselves by the type of dose-effect relationship and are dependent on the analysed dose range.

Whilst there can well be differences regarding model effects in the medium to higher dose range, these will mainly disappear in the lower dose range. Furthermore, examples of empirical combined effects show a match of observed and calculated effects in the lower dose range. In the medium and higher dose range not seldomly stronger (or also weaker) effects than were expected on the basis of the models are observed.

The medium and higher dose range may show combined effects that cannot be observed in the lower dose range, i.e. deviations from the model effects dose-additivity and independence. Of these effects those combined effects are interesting which exceed corresponding model effects e.g. super-additive effects or larger effects than would be expected for independent combined effect. The latter is due to special toxico-kinetic or toxico-dynamic processes, which explain the rarer cases of spectacular increases in combination. In these few cases the combinations react partly with much stronger damaging effect than the individual single components, which has to be considered for corresponding regulatory procedures.

Wherever combined effects established on the basis of models differ remarkably from each other e.g. in the case of multiple exposures, one will, given toxic effects, observe stronger effects in the dose-additivity model compared to the independent model. If the type of combined effect is unknown, the dose-additivity model can be considered as a "worst case" scenario when evaluating the effect of serious or dangerous substances.

Due to the theoretical considerations and the analysis of empirical combined effects of *unidirectional agents* e.g. medicine, alcohol and malformation causing substances the following situation evolves:

Frequently effects of combined exposures in the medium and higher dose range are larger than the effect of the component with the stronger effect. Generally we do not find any amplification effects in the lower dose range. For anti-tumour substances and also teratogenes with a different molecular target the threshold doses of a substance A in the presence of B is not reduced. Dose-additive combinded effects are to be expected (e.g. in the case of hormones and partly with regard to carcinogenic agents).

In addition to the described toxico-dynamic combined effects, toxicokinetic interactions are of significance, e.g. one substance halting the reduction of another substance. The models described above are not suitable for the description of kinetic combined effects, but these interactions deserve major interest, since they can lead in rare cases to spectacular amplification effects.

Combined Effect of Radiation and Substances

In the case of exposure to ionising radiation, it is very often the case that an assessment of the dose in the target tissues and cells can be better conducted than in the case of chemical substances. Since, in addition, there is a relatively high amount of experimental data regarding combined exposures with the inclusion of ionising radiation, these investigations have been given exemplary treatment in this study. The dose limits for ionising radiation at the workplace and in the environment are set out in such a way that non-stochastic, deterministic effects of radiation can be avoided. Therefore, only stochastic effects of radiation (genetic mutation and cancer) have to be taken into account in the area of dose limits and lower doses. This criterion also has to be fulfilled in the case of combined effects. Consequently, those agents are of interest which can have an interaction on the various stages of the development of stochastic effects of radiation following corresponding exposure. The numerous experimental investigations and epidemiological studies have led to the following results with regard to combined effects between ionising radiation and multiple chemical substances:

- Genotoxic substances, which like ionising radiation cause the initial DNA-damage in the case of development of cancer and mutations, generally lead to additive effects following combined exposures. This is particularly true in the low dose range.

- Substances, which impair the repair of DNA damage following exposure to ionising radiation, can cause super-additive effects. This is true, for example, of heavy metals, caffeine and various chemo-therapeutics. However, relatively high concentrations of substances have to be reached for this kind of suppression of enzyme systems of DNA repair to occur.

- Substances, which reduce the primary radical reactions following radioactive impact can reduce the effect of the exposure. This is particularly true in the case of radicalscavengers, e.g. substances containing sulphhydryl groups.

- Substances which alter the regulation of cell proliferation subsequent to radiation exposure can cause super-additive effects. In these cases substances can shorten radiation-dependent delay processes in the proliferation cycle of the cells, which normally allow repair processes and thus these substances reduce DNA repair. In addition, substances which above all have a hormonal effect, can stimulate cell proliferation and on the basis of mechanisms of this kind, amplify the development of cancer following radioactive exposure.

For interactions between the development of the effects of radiation and substances, the sequence of exposure in time is of considerable significance. For the influencing of primary processes of damage development the exposures to ionising radiation and to the appropriate chemical substances have to be close together. This is also true for those substances which reduce DNA repair. They have to have an effect on the exposed cells within only a few hours of radiation exposure. In contrast, substances which lead to amplification of the development of cancer by stimulation of cell proliferation can still cause a super-additive effect following substantially later exposure. The varying experimental investigations, as part of which dose-response relationships have been worked out, have shown that super-additive effects in general, only occur in the medium to high dose range. In the low dose range mainly additive effects result. It must also be taken into account here that all exposures to chemical substances are accompanied by low dose ionising radiation from natural sources.

Investigations of the combined effects following exposure to densely ionising radiation (neutrons, alpha-radiation and others) with toxic substances have led to the result that substances, which inhibit DNA-repair lead to a lesser extent to super-additive effects given these combinations. In contrast, substances which stimulate cell proliferation cause super-additive effects even with densely ionising radiation. Therefore, in general super-additive effects between chemical pollutants and ionising radiation only have an effect if specific interactions occur between the pollutant and the various stages of development of the effect of radiation. In general, a relative increase in the radiation risk by a factor of 2-3 is reached. In very few cases does this effect extend beyond a factor of 5.

The analyses of epidemiological investigations have uncovered super-additive effects in the case of persons exposed to radiation who are also heavy cigarette smokers. Here too, high levels of exposure are necessary for a super-additive effect to occur in the proportion of lung tumours.

Overall the investigations of combined exposures with ionising radiation indicate a whole series of possible exposures which can lead to super-additive effects. A number of ideas with regard to the effect mechanisms, which permit extrapolation for further possible combinations, could be worked out. However, these super-additive effects have only been observed in the medium and high dose ranges. Therefore the extrapolation of this data in low dose ranges would have to be validated further.

Combined Effect of Substances

The number of possible combinations of chemical substances is legion, the portion of exposures which actually occur in the everyday life of man and in the environment is still enormously big. This clearly places emphasis on the purely chemical combinations compared to more simple systems such as radiation and medication, as well as exposure at work and requires differing strategies for determination, evaluation and regulation.

The fact that most of the limits for risk minimisation or avoidance have been fixed with regard to chemical substances, is also an expression of the variety which is different from other systems. However, the criteria used in the determination of these limits vary to an extraordinary degree. Individual categories, perhaps those having existed longer, are orientated along the lines of "effect thresholds", others follow minimisation principles, whereby the scope of "precaution" to be shown moves within broad limits with the following result: The "safety margins" vary from zero to close to a million. The reasons for this are numerous: Differences in the traditions of academic disciplines dealing with the matter, uncertainties in the evaluation of scientific risk data, in socio-political demands, in the acceptance of (residual) risks, and so on. Given broad margins of increased factors of safety in various types of exposure limits, the enticing attempts presented again and again on the part of administration to use simple calculation models to regulate combined effects, which additively aggregate limiting value fragments according to their share in mixtures, are out of the question.

Literature available on toxic effects of chemical substance mixtures reveals that the subject has been processed in a non-systematic manner not covering all areas. Very heterogeneous formulation of questions and above all the use of very high doses irrelevant to questions regarding limit values, render the comparison of data for the purposes of working out mutual regularities more difficult. For this reason, we attempt in this article to sort the description of known facts relating to the combined effects of chemical substances according to mechanistic models – whilst not claiming completeness.

Substances in mixtures may attack the same or different target organs, function according to the same or differing mechanisms and become effective in an unchanged state or following enzymatic transformation; and this independent from each other or under mutual influence (interaction).

Interactions, by far the more important category for combined effects, can take place at all stages of the movement of substances within the organism: in resorption and distribution, metabolisation, infiltration into cells, at the (biochemical) target structure in the cell, in the repair of damage incurred. Depending on the direction of the influence of action, completely independent, additive, sub-additive or super-additive effects are to be expected in combination. Super-additive effects are of particular significance with regard to the question of setting limit values for combinations.

It is possible to derive different kinds of scenarios from the mechanistic basic factors as the basis for possible determinations of limit values, which permit predictions with regard to interactions and their consequences for combined effects:

- Substances in combination attack as such, i.e. in unchanged form various target structures independently of each other and generate various damaging effects. With regard to the relative specificity of the effects of harmful substances this could well be the most frequently occurring case. In this regard, effect-related limit values for individual substances do also have validity in combination.

- In unchanged form and independent of each other, substances generate the same effects at the same target structures. Addition of the effects is assumed here. Limit values for individual substances potentially do not provide sufficient protection if they are effect-threshold orientated. A reduction thus might be necessary.

- Substances have effect only after enzymatic biotransformation. If one component restricts the development of the other's form of effect a weakening of effect is to be expected. Existing limit values for individual substances afford sufficient protection.

- If one substance restricts the enzymatic inactivation of another, it is possible that a strong increase in effect can come about – provided the degree of detoxification is high. This combination, although rarely occurring, is the most important for practical regulations since it is possible that super-additive increases may occur.

It is theoretically possible that one active substance can, through induction of the bio-activation enzymes of the other, increase its effect. Since limit values for these substances, such as tumour promoters, are generally set below the threshold values for induction, this case does not play a fundamental role in the practical field.

The description of the existing literature, according to this guideline, separates conventional toxic substances ("reversible" effect) from genotoxic ("irreversible" effect causing mutations and cancer), since the latter follow other laws with regard to dose and effect: No threshold doses can be estimated. For example, the results of the examination of complex, undefined mixtures are presented and compared with those purposefully combined. These are checked with regard to the correctness of predefined hypotheses. The forecasts theoretically derived according to the above schema are essentially confirmed by existing literature; apparent contradictions can be explained. Valid predictions, however, can only be made if the toxico-kinetic and toxico-dynamic characteristics of the components of a mixture have been compiled to a sufficient degree beforehand. Depending on the place and type of attack the rules regarding independence or interaction are confirmed as sound. In the case of interactions the essential general rule emerges: As the dose decreases, additive/super-additive effects become weaker, in the area of limit values they are mostly no longer detectable. Exceptions are based solely on insufficient knowledge about the effect characteristics of the action for individual components within mixtures.

Combined Effects on Plants

Ozone, the sulphur oxide compounds and nitrogen emissions currently pose the greatest dangers for vegetation in Central Europe and in North America. Extensive experimental and epidemiological findings also exist with regard to the effects of these contaminants as individual components. At the same time, there are guideline values for the aforementioned pollutants as individual components which have been derived by various expert committees with an aim to protecting vegetation. For these reasons these three components have been selected as examples for the evaluation of combined effects in ecotoxicology.

As well as sub-additive reactions, combinations of these pollutants cause additive and super-additive reactions in plants. In the case of weak damaging effects it is possible that additive effects can give an underestimation. Almost all combinations result in combined effects, which (to a large extent) correspond to independent effects, thus indicating a lack of any particular interactions. One exception is the combination of SO_2 and NO_2, where often a synergism in the context of a super-additive effect has been found. The cause of this intensifying interaction is being discussed.

The differing effect characteristics of the selected components (SO_2 and O_3 phytotoxic, SO_2 with lack of sulphur and the N-compounds, trophic up to a certain load level) have the consequence that even given low shifts in concentration, qualitative changes occur in the reaction of the plants.

The derived guideline values for the protection of vegetation against mixed emissions are based on the results of three methodological approaches:

- Comparative experimental investigations on the effects of two or three components either individually or combined;
- Comparative epidemiological investigations in areas with high exposure values with regard to the effect of filtered and unfiltered air;
- Models to derive patterns of concentration over time which are still tolerable.

The results of these experiments do not suffice to determine guideline values for combined exposures with the components selected, which are below the existing guideline values for the individual components:

- When determining the guideline values for individual components the responsible expert committees more or less explicitly took results from experiments with combined exposures into account.
- The lowest concentrations of pollutant gases applied in the combination experiments which still led to sub-additive, additive or super-additive effects were each time over and above the guideline values derived for the individual pollutants to protect vegetation.
- Plants, when subjected to exposure in chamber systems are mostly exposed to a higher speed of deposition, i.e. a higher effective dose given the same concentration of pollutant as outdoors. Because the derivation of guideline values for individual components is essentially based on experimental and epidemiological experiments in chamber systems, a safety margin should naturally be contained in guideline values obtained in this manner.

Risk perception

From a psychological and sociological point of view, the structures and processes of individual perception of risks and the ways these are dealt with socially, should be examined more closely. Attention is directed here at the level of perceptions and associations with the help of which people understand their environment and on the basis of which they carry out their actions; one speaks of ‘constructed reality’. The following patterns of conception characterise the scope of significance of risk as a part of intuitive perception:

- *Risk as a threat*: The notion that an event can affect large portions of the population concerned, at any point in time, creates the feeling of being threatened and powerlessness. The extent of the perceived risk in this case is a function of three factors: *of the randomness of the event, of the maximum extent of the damage expected and of the time span available to avoid the damage.*

- *Risk as a stroke of fate:* Natural disasters are mostly viewed as unavoidable events, which admittedly have devastating consequences but are seen to be “whims of nature” or “the will of God” (in many cases *also as* mythological punishment from God for collective sinful behaviour) and are therefore beyond human intervention.

- *Risk as a challenge of one’s own powers:* In this understanding of risk, people take risks in order to challenge their own powers and provide them with a taste of triumph after successfully winning a battle against the powers of nature or other risk factors. The fundamental incentive to participate is to ignore nature or co-competitors and to master self-created risk situations through one’s own behaviour.

- *Risk as a game of chance:* If the principle of chance is recognised as a component of risk, then the perception of stochastic distribution of payouts is the closest to the technical-scientific concept of risk. Now this concept is almost never used in the perception and evaluation of technical risks. It refers to financial risks.

- *Risk as an early indicator of dangers:* According to this understanding of risk, scientific studies help to discover insidious dangers early and uncover hidden relationships between activities and/or occurrences and their latent effects. Examples of this usage of the notion of risk can be found in the cognitive coming to terms with low doses of radioactivity, food additives, chemical pesticides or the genetic manipulation of plants and animals.

Many people perceive risks as a complex, multi-dimensional phenomenon in which subjective loss expectations (not to mention those calculated statistically) only play a subordinate role, whilst the context of the risky situation, which has an effect in the different meanings of risk perception, substantially influences the degree of the risk perceived. This dependency of risk evaluation on context is the decisive factor. This dependency on accompanying circumstances is not random but follows certain regularities. These can be investigated by using *specific* psychological investigations. Investigations with regard to the context conditions of risk perception have thus been able to identify the following factors, amongst others, as being relevant:

- Familiarity with the risk source;
- Willingness to take risk;
- Personal ability to control the degree of risk;
- Ability of the risk source to cause disaster;
- Impression of an even distribution of benefit and risk;
- Impression of reversibility of risk consequences;
- Trustworthiness of the information sources.

The significance of these qualitative characteristics for the evaluation of risks offers an obvious explanation for the fact that precisely those risk sources which were deemed to be particularly low risk in the technical risk analysis, met with the greatest resistance amongst the population. Risk sources which are viewed as controversial, such as nuclear energy, are particularly often associated with negatively laden attributes, whilst in contrast leisure time risks carry more positive attributes.

Until now it has not been investigated empirically how the indicated reaction patterns change in the case of combined risks. In order to fill this research gap a representative survey was carried out within the framework of the project in 1998 amongst the population of the federal German state of Baden-Württemberg. The survey involved a representative cross-section of 1,500 adults. The main emphasis of the survey was the perception and evaluation of technology within the population. Within the scope of the survey, the significance of environmental risks in general and of combined environmental risks in particular were researched.

In the evaluation of combined environmental risks a broad gulf was revealed between the opinion of most experts and the lay individuals surveyed. Over two-thirds of those surveyed were convinced that super-additive effects are generally to be expected given the interaction of several pollutants. Just under a quarter (23,8%) were indifferent in their answer and only 9,6% rejected this assumption. The reason for this clear answer can on the one hand be derived from everyday experiences with medium or high doses of medication or stimulants. On the other the typical risk aversion for the risk type "indicator of damage" plays a fundamental role, particularly the intolerance of any further uncertainty which exists. Because of this attitude of expectation, it is indeed understandable that most people believe reports about damage to health through combined environmental pollutants and that the scientific experts and regulatory authorities will find it difficult to convince the sceptical public of the opposite.

Possible effects on health are not only triggered by the pollutants but arise as the result of psychological or psychosomatic processes. Of special significance here are those psychosomatic reactions which have come to be known in literature as part of the category "multiple chemical sensitivity syndrome". Public perception of this syndrome is contributing towards the popularisation of an effect connection. A vicious circle thus begins: The perception of exposures, above all to combined pollutants, causes fear and uneasiness amongst the observers. In turn, this uneasiness leads to psychosomatic reactions in some individual cases. *These* reactions are observed and are deemed as evidence of the supposed causal connection between emissions and damage to health.

In addition to this, combined effects are suitable as topics of political mobilisation. For one thing, they are the subject of press coverage since health and the environment are favourite media topics. Due to the perception of real syndromes, the decline in expert credibility and the discrepancy between risk researchers and lay persons, public pressure is mounting for politics to regulate more vigorously. This pressure leads of course to counter pressure from those groups which would be negatively affected by more stringent regulation. The row has the effect of polarising society.

Economic Aspects

Cost-efficient standards: Environmental policy should on the one hand guarantee that certain load limits be adhered to with regard to man and the environment. On the other hand it should also pay heed to the aspects of cost-effectiveness. Environmental economics emphasises the significance of the principle of cost-effectiveness. It has worked out in the case of single pollutants that economic instruments (environmental taxes and tradeable permits) enable a more cost-efficient form of environmental protection than legal regulation and should therefore be applied there. In the case of multiple pollutants, however, the objective of economic efficiency has additional significance. Under these conditions, at least two substances are responsible for one specific damage. If a load limit has been determined, it then has to be clarified as to which of the pollutants is to be regulated against and to which degree. From an economical viewpoint this decision should be made according to the criterion of cost-effectiveness. The limit values should therefore be determined in such a manner that the total economic costs are as low as possible.

Damage to the environment may cause damage to health, material damages (including losses in production), as well as ecological damage. Load limits are derived from objective notions with regard to the extent of permissible damage in these areas. Guideline targets of this kind provide the measure for limit values in environmental policy. Environmental policy's central guideline target is securing the health of the nation, whilst health itself is subject to delimitation in a certain way and can be measured in the light of the relative frequency or severity of an illness. When considering cost effectiveness, the guideline targets of environmental policy are taken for granted.

It is assumed that one guideline target is compatible with varying combinations of agents. The possibility of substituting the agents (A and B) should therefore exist. A certain additional quantity of A would, according to the relative specific harmfulness of the substances, require a certain reduction in the quantity of B. The type of combined effect (additivity, super- and sub-additivity) has bearing on the relationship of the specific harmfulness of the substances. The opportunity presents itself to make a selection according to aspects of cost from amongst the bundle of ecologically equivalent combinations. So as to keep the costs of environmental protection as low as possible, agents where the reduction thereof is associated with relatively low costs and/or relatively strong relief effect should be reduced to a greater extent than those substances with relatively high abatement costs and/or relatively low relief effect. Because costs typically increase progressively with increasing levels of pollutant abatement it would mostly be appropriate to impose limitations on all substances concerned. One should not concentrate on one particular substance even though it may be the main cause of damage. In the exceptional case of a substance which is very cheap to reduce and provides high levels of relief on reduction, it can, however, also be efficient to concentrate on this substance.

Whether the effects of the agents in combination become stronger or weaker or whether they are the same as when occurring separately, has bearing on the level of cost of environmental policy. Environmental protection costs increase in the case of super-additivity of effects in comparison to additivity. The strengthening of individual effects is the same as an increase in costs. In order to meet the same guideline target as for additivity, it is necessary to set stricter environmental standards for the agents, which in turn causes higher costs. There is then a tendency in the political process for it to become more difficult to meet any set objective. If, on the other hand, two substances combined actually weaken damaging effects, this is tantamount to cost-free abatement. Given an additive relationship, the limiting values would have to be set lower to achieve the same protective effect as for sub-additivity. Meeting a guideline target is linked with less strict requirements and consequently with lower environmental costs. High costs of environmental protection are a fundamental obstacle to enforcing strict environmental standards. Because of these varying implications with regard to cost, it is important to establish clarity with regard to the type of effects.

Cost comparisons are only possible in the case of quantitatively formulated guideline targets (maximum permissible degree of health risk, upper limits for global warming, avoidance of summer smog, amongst others) and standards. This underlines the general demand on the part of the economy that legislative organs should set targets with a greater emphasis than to date on quantitative rather than qualitative criteria ("Avoidance of damaging environmental effects" or "state of the art of environmental precautions").

Measures: With the aid of an appropriate set of instruments (laws, charges, tradeable permits, voluntary agreements and subsidies) it must be ensured that the limit values set are adhered to. The special requirement of the use of these instruments in the multiple pollutant case is to bring about the efficient abatement structure. Not all instruments are always suitable for achieving this in the same way. Tradeable permits have advantages in the case of combined effects with linear additivity. If environmental charges or legal standards are used, the efficient limiting values are to be directly set as the target values. The task becomes easier in the case of tradeable permits and linear, additive exposure. Knowledge of the structure of abatement costs is not necessary here. All that needs to be known is a combination of emission caused damages which is compatible with the guideline target and the specific harmfulness of the substances. By issuing tradeable permits to the amount of emissions recognised as permissible which can be exchanged amongst themselves in the ratio of the specific levels of harmfulness it can be achieved that an efficient structure will result through adjustments within the economy itself.

In the case of non-linear combined effects this advantage with regard to tradeable permits solutions no longer exists. In these cases no special instruments are immediately evident. In which way certain protective and precautionary targets can best be achieved then depends, as is the case with single exposures, on the respective problem.

Decisions under uncertainty: In those areas where relatively little is still known about combined effects, any decisions with regard to limit values are to be made under uncertain conditions. Economic-decision-making models help reveal the relevant determining factors for economically rational decisions (relative harmfulness and relative abatement costs, extent and measurement of uncertainty as well as risk evaluation). This is shown for differing degrees of uncertainty (stochastic model, fuzzy-model and uncertainty model). The analysis clearly shows that even given a limited level of knowledge, it is possible to make rational decisions. Therefore, in the process of determining limit values decision making theory should be applied.

Political conclusions: Because in practice to date the single substance consideration has predominated and cost-efficiency considerations hardly play a role at all in multi-substance phenomena, opportunities present themselves for an improvement in policy. In the course of a reform it can prove particularly advantageous to extend a policy which until now has only been intended for one pollutant to include others (for example climate protection policy) and to alter the relationship of existing (single substance) limit values for all agents contributing towards any specific damage. Even if very little information is available about the effects of ecologically equivalent combinations of agents, the economic approach is indeed meaningful because if, for example, only three ecologically equivalent combinations of several constituent pollutants are known, it is nevertheless possible to make a selection according to their economic costs.

If several pollutants occur both in combination as well as separately, a policy of differentiation should be pursued, which in the case of combined exposures works with specific limit values and which otherwise uses individual values (see the part on legal questions as well).

Generally it will be most efficient to include all significant co-causative agents in the policy. In special cases, however, concentration on a single pollutant may be the most cost-advantageons. In this case, there is a possible conflict with the objective of just distribution of burden, according to which parties causing environmental damage are to be called to account. The generality-demand is part of the normative reason for the polluter-pays-principle. One-sided allocations of burden are particularly problematic if companies competing directly with each other are affected differently thus distorting the competition. One possible solution of the conflict between efficiency and just distribution is that financial compensation be introduced among burdened and exempted parties. All exempted parties would have to be committed for side-payments.

Legal Questions regarding Combined Effects

Until now, legal questions regarding combined effects of substances and radiation do not play a central role in German environmental law. In particular, there is a lack of any discussion in jurisprudence of this question. Because of its constitutional obligations to protect, the state is bound to provide comprehensive protection of the individual against dangers and risks caused by environment pollution, which itself also includes combined effects. However, there is a broad margin of political discretion particularly in the area of purely precautionary measures.

The individual media-related environmental laws contain no express regulation pertaining to combined effects. However, with regard to the general formulations of legal purpose and powers to regulate they do not preclude consideration of such effects. In laws governing the use of chemical substances the law governing the manufacture and marketing of drugs expressly demands consideration of the combined effect of multiple substances. The law on chemicals relates to the individual substance with regard to determining dangerous properties but in contrast, with regard to regulation, combined effects may be taken into consideration (bans and restrictions, classification, labelling and packaging). The same is true of the food and consumer goods law.

Sub-legal regulations in the form of limit or guideline values, trigger values and classification rules often take combined effects into account. In doing so they include such effects in the safety margin, view a substance as characterising, or assume concentration or dose-additive effects; often there are correction possibilities should there be a basis for super-additive or antagonostic effects, however, without therebeing any obligation to do so. Ambient quality values and emission and/or trigger values for carcinogenic and certain other particularly dangerous substances, maximum workplace concentration values in industrial safety and regulations regarding the classification of preparations as well as mixtures posing a threat to water, are of particular significance.

Questions with regard to allocating the regulatory burdens of tackling combined effects are the subject of discussion particularly in environmental liability law. Private liability law has developed two allocation models, namely proportional liability and joint liability with internal contribution rules, both of which are transferable to other cases of "retrospective" liability; this can be seen in the regulation of polluter responsibility under the federal soil conservation act. In the case of "prospective" regulation, one mainly follows the principle of priority. The concept of a "community of emitters" with joint responsibility is fundamentally rejected.

In the United States, Switzerland and the Netherlands combined effects are given more extensive consideration in parts of environmental law than in Germany.

It is evident that knowledge with regard to the type and extent of combined effects is as yet insufficient. The legal regulations regarding the determination of combined effects should therefore be improved. This requires, above all, an amendment of chemical legislation at European Union level. The manufacturer should be obligated to investigate any indication of combined effects in the base set of testing; these findings would then have to be expanded upon if necessary on the basis of supplementary test requirements. The testing of old substances should also be amended accordingly.

It must be taken into account from the legal point of view that when regulating combined effects, constitutional requirements do not compel the state to seek a solution which is “optimal” in substance. The application of the principle of protection (defending against danger) and of the precautionary principle (taking precautions against risk) permit appropriate solutions to be found if their constitutional limitations are heeded. Fundamentally, a distinction has to be made between proven and assumed combined effects. Given mere suspicion of combined effects it is possible to proceed along the lines of the precautionary principle. However, this presupposes a minimum degree of plausibility with regard to the suspicion. Purely speculative assumptions about combined effects do not suffice and, in any case, there have to be correction possibilities in place in case no combined but instead completely different kinds of effects arise from joint exposure to several substances. Consequently, global risk minimisation strategies are problematic without any basis for assuming combined effects. In so far as there is reason to believe that combined effects exist at all, it is essentially permissible to assume the dose-additive effect model or else independent combined effects. Sufficient correction possibilities are, however, required in case other types of effects, in particular those of the super-additive kind, are established.

Particularly worthy of consideration as regulative strategies are individual case evaluations, safety margins, limit values for combined effects and limitations of dispersion. A broad degree of executive discretion exists with regard to the selection and tailoring of these strategies. Out of all possible strategies for the regulation of combined effects it is individual case assessment which represents the fundamentally superior solution. However, for pragmatic reasons it should not hinder the search for global solutions.

Special (additional) safety margins for combined effects added to single substance-related limit values are in principle an acceptable strategy if we are dealing with substances with a threshold value. However, this requires that the safety factor affords an appropriate level of protection should the substance occur on its own and that the substances very frequently appear in a certain combination. In principle, as a typifying solution, they meet the requirements of the principle of proportionality. However, in the low dose range, they can lead to an excess of precaution.

If one component of a mixture is so dominant that it characterises the whole mixture, no actual regulation for combined effects of the mixture is required; the limit value for the individual substance shall prevail.

Generally speaking, it is limit values (and values approximate to limit values, such as trigger values and classification regulations) which should be preferred for combined effects. This is particularly true in the area of protection of occupational health as well as in the case of substances without a threshold value. In the case of known combined effects it is entirely possible, given the present level of scientific knowledge, to perform limited quantification. As for the rest, the regulator can assume the prescriptive model of dose-additive effects or else independent combined effects, so far as appropriate correction possibilities are made a proviso.

Global limitations on emissions (e.g. minimisation) are acceptable if they are used on their own or in addition to other strategies, even for single substance risks.

With regard to the allocation of the reduction burden (addressing measures to particular actors), other measures are to be considered in addition to the option solution tailored to combined effects caused by a single source. These would include in particular, quota systems, compensation solutions (burden of reduction for one source with obligation to pay compensation on the part of the other), as well as the priority principle. Since the Constitution does not call for a “balanced” environmental policy and the principles of equality and proportionality only set extreme limits, there is a broad margin of political discretion with regard to allocation.

Wherever possible an option solution should be chosen which allows the source to decide with regard to allocation. This of course presupposes that several combinations of the substances in question are acceptable from point of view of both health and the environment. As for the rest, the postulate of equitable distribution demands that more emphasis be placed on the polluter-pays principle – perhaps through the use of quotas with guaranteed ”burden margin”. As an alternative, which at the same time takes aspects of economic efficiency into consideration, obligations to reduce emission levels combined with compensation on the part of other sources involved could also be tried. Regulatory models related to the point in time at which dangerous activities were started (e.g. priority principle) should only be considered if other solutions fail.

With regard to the relationship between regulation and allocation, it has to be borne in mind that the “logic of regulation” (environmental policy decision-making) limits the “logic of attribution” (decision-making regarding as to whom the measures are addressed). Not all of the possible regulatory models are compatible with the attribution models considered. It is individual evaluations and special limit values which are most favourable in this regard. These can be linked with a multitude of attribution models.