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Risk assessment of peak exposures to carcinogenic substances
Report of a workshop

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Abstract

Short-term exposures to relatively high concentrations of chemical substances are a regular cause of concern, this holds especially for carcinogens. A report published by the Health Council of the Netherlands and some additional publications showed that tumor induction can result from peak exposures. The possibilities for the development of a decision tree for the risk assessment of peak exposures to carcinogenic substances were discussed by scientists and policy makers of several Ministries. A gradual development of a categorical decision tree by a multidisciplinary working group was endorsed. The workshop came up with a number of issues that should be addressed by the working group.

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Samenvatting

Kortdurende blootstellingen aan relatief hoge concentraties of doses van chemische stoffen geven regelmatig aanleiding tot bezorgdheid. Carcinogeniteit is vooral vanuit sociaal-maatschappelijk oogpunt vaak een bron van zorg in dergelijke situaties. Derhalve is de vraag relevant in hoeverre een eenmalige kortdurende blootstelling aanleiding kan geven tot tumorvorming en of dit risico kwantitatief kan worden ingeschat. Het onderhavige project richt zich op de mogelijkheden voor de ontwikkeling van een beslisboom op basis waarvan het carcinogeniteitsrisico kan worden ingeschat in acute blootstellingssituaties.

Basis voor het huidige project vormt een rapport uit 1994 gepubliceerd door de Gezondheidsraad. De centrale vraagstelling hiervan luidde: hoe verhoudt het geschatte carcinogeniteitsrisico na piekblootstelling aan een genotoxisch carcinogeen zich relatief ten opzichte van het carcinogeniteitsrisico bij levenslange blootstelling aan een zelfde cumulatieve dosis? Het rapport kwam tot de conclusie dat eenmalige of kortdurende blootstelling aan carcinogenen tumorvorming kan induceren. Het rapport richtte zich op de afleiding van een Dose-Rate Correction Factor (DRCF), gedefinieerd als de factor waarmee de tumorincidentie, gerelateerd aan een specifieke cumulatieve dosis van een carcinogene stof toegediend met een lage dagelijkse dosis, moet worden vermenigvuldigd om de tumorincidentie bij een hoge dagelijkse dosis te schatten. Met behulp van theoretische modellen werd een maximale waarde voor de DRCF afgeleid van 7; dit gold voor de situatie dat een jong kind werd blootgesteld aan een initiator. Op basis van dierexperimenten kwamen de auteurs tot een maximale DRCF van 8,3. Kennis omtrent verzadiging van metabole processen en van DNA-repair mechanismen werd cruciaal geacht voor de afleiding van een DRCF. PBPK-modellering werd aangemerkt als een waardevol instrument om de juiste interne dosimetrie vast te stellen en om de biologisch effectieve dosis af te leiden.

Halmes *et al*. (2000) vergeleken resultaten van ‘stopexposure’ experimenten met die van chronische blootstellingsexperimenten voor 11 stoffen. De data waren te beperkt om eenduidige conclusies te kunnen trekken. Het carcinogeniteitsrisico bij kortdurende blootstelling kan zowel onderschat als overschat worden bij lineaire extrapolatie vanuit chronische experimenten, maar vaker zal van onderschatting sprake zijn. Bij twee stoffen werd organotropie waargenomen: specifieke tumoren werden wel gevonden in stopexposure experimenten, maar niet in experimenten met chronische blootstelling.

Een interne discussie binnen het RIVM benadrukte de problematiek van de factoren betrokken bij de risicoschatting voor carcinogeniteit bij een piekblootstelling. Onderwerpen die nader uitgewerkt dienden te worden waren inschatten van de meest geschikte dosimetrie met behulp van PBPK-modellering, identificeren van levensfasen gedurende welke mogelijke doelwitorganen een verhoogde mate van celproliferatie ondergaan en de mogelijkheid om gebruik te maken van de resultaten van studies met de neonate muis.

Tijdens een workshop werden de beleidsmatige wenselijkheid en de wetenschappelijke mogelijkheden om te komen tot een beslisboom voor de risicoschatting van eenmalige blootstelling aan carcinogene stoffen bediscussieerd. Hiertoe waren zowel wetenschappers als beleidsmedewerkers van diverse ministeries uitgenodigd. Inleidingen werden verzorgd door beleidsmedewerkers van de Ministeries van VWS en VROM en door wetenschappers, gevolgd door groepsdiscussies en uiteindelijk een plenaire discussie. Geconcludeerd werd dat carcinogeniteit een relevant eindpunt is in de risicobeoordeling bij acute blootstelling. Er bestond wel behoefte aan een duidelijke definitie van piekblootstelling. Het ontwikkelen van een beslisboom werd ondersteund maar gezien de complexiteit van het onderwerp werd een trapsgewijze aanpak wenselijk geacht. Een categorale beslisboom biedt mogelijkheden om op een relatief eenvoudige wijze differentiatie aan te brengen tussen carcinogenen. Hiervoor is een multidisciplinaire aanpak noodzakelijk. Bij de ontwikkeling van een beslisboom zal specifiek aandacht worden besteed aan de extrapolatie van een chronische blootstelling naar een acute blootstellingssituatie. Het kan de voorkeur verdienen om direct over de tijd te extrapoleren van chronische blootstelling naar een eendaagse blootstelling, en niet via de afleiding van een geaccepteerd risiconiveau voor de mens bij levenslange blootstelling. In dat geval zullen de dosisafhankelijkheid van bijvoorbeeld het metabolisme en DNA-herstelmechanismen en van organotropie minder van belang zijn voor de extrapolatie.

De mogelijkheden voor de opzet van een beslisboom zullen worden onderzocht door een multidisciplinaire werkgroep bestaande uit betrokkenen afkomstig uit verschillende instituten. Het werkingsmechanisme en het DNA-herstelmechanisme, het basisconcept dat tumorincidentie gerelateerd is aan de cumulatieve dosis, mogelijke levensfasen met een verhoogde mate van gevoeligheid voor tumorvorming en de mogelijkheden van het gebruik van theoretische modellen zijn onderwerpen die aan de orde zullen komen. De beslisboom zal aan de hand van modelstoffen worden gevalideerd.

Summary

Short-term exposures to relatively high concentrations or doses are a regular cause of concern. Since carcinogenicity is often of great social relevance the question arises whether a single (one day) exposure to a carcinogenic substance can give rise to tumour development and, if so, whether this risk can be quantitated. The present project focussed on the development of a decision tree for the evaluation of the carcinogenic risk in case of acute exposure.

Starting point was a report published in 1994 by the Health Council of the Netherlands. The key question was 'What is the estimated cancer risk of peak exposure to a genotoxic carcinogen *relative* to the cancer risk of the same total dose of this carcinogen distributed over an entire lifetime?' The authors concluded that short-term or single exposure could give rise to tumour formation. The report focussed on the derivation of a Dose-Rate Correction Factor (DRCF) defined as 'a factor by which the tumour incidence caused by a specific dose of a chemical carcinogen at low dose rates is multiplied to derive the tumour incidence at high dose rates'. For this purpose experimental studies as well as theoretical approaches were reviewed. Theoretical models calculated maximum values for the DRCF of up to 7 for a young child acutely exposed to an 'initiator' or first-stage carcinogen. A maximum value of 8.3 was calculated from animal experiments. Saturation of metabolic processes and of DNA-repair mechanisms may crucially influence the DRCF for peak exposure to genotoxic agents. PBPK-modelling could be helpful to identify the appropriate internal dose metrics and to estimate the biologically effective dose.

A paper by Halmes *et al.* (2000) compared stopexposure with lifetime exposure experiments for 11 substances. The data were considered too scarce for clear overall conclusions. Linear extrapolation from lifetime exposure experiments to a short-term exposure can lead to both underestimation and overestimation of the cancer risk, but may result more often in an underestimation. For two substances the phenomenon of organotropism was observed, *i.e.* tumours were observed in the stopexposure groups, while chronic exposure did not induce tumours in these sites.

The difficulties of the evaluation of peak exposure to carcinogenic substances were acknowledged during a discussion within the RIVM. Suggestions for study objectives included PBPK-modelling for the estimation of an appropriate dose surrogate, identification of life stages with an increased cell proliferation rate in target organs, and the use of neonatal mouse data.

A workshop was organised to discuss the (governmental) advisability and (scientific) possibilities for the development of a decision tree for the evaluation of a single exposure to a carcinogenic substance. Both scientists and policy makers from several ministries were

invited. Introductory presentations by policy makers and scientists were followed by group discussions and a plenary session. Carcinogenicity was considered to be a relevant endpoint within the present context. A clear definition of peak exposure was badly needed since different definitions appeared to be operable. A decision tree was regarded as a practical tool, but should be gradually developed considering the complexity of the subject. A categorical decision tree may offer possibilities for a relatively easy differentiation between carcinogens. In either way, the development of appropriate classification criteria will demand a multidisciplinary approach. Specific attention will be paid to the extrapolation of a lifetime carcinogenic risk to short-term exposures. It may be preferable to extrapolate directly over time from a chronic animal experiment to a one-day exposure instead of starting from an accepted human risk level. Aspects like dose-dependency of metabolism and DNA-repair mechanisms and organotropism may then become a minor issue.

A working group with experts from different institutes will be established to explore the possibilities for the development of a straightforward and transparent categorical decision tree. Elements that will be considered are mechanism of action and of DNA-repair, the basic concept of tumour incidence being related to cumulative dose, life stages at which subjects may be at extra risk, and the possibilities of theoretical models within the present context. The decision tree will be validated with model-substances.

1. Introduction

The risk assessment or limit setting of exposure to chemical substances is mainly focussed on preventing adverse health effects after repeated (mostly lifetime) exposure to relatively low concentrations. Also the governmental regulations concerning the admittance of substances to the market or the conditional restrictions of exposure are generally aimed at long-term exposures. However, short-term exposures to relatively high concentrations or doses are a regular cause of concern. For instance, acute exposures may occur as a temporarily exceeding of specific health-based standards (pesticide residues in food, air emissions), through contamination of food, usage of biocides, or due to chemical incidents. Further, insight in the risk of adverse health effects after acute exposures are also of importance in spatial planning, exposure during fires, and the derivation of Intervention Levels for hazardous substances within a contingency plan for emergency responses.
Since in certain situations acute exposures are inevitable, standards for acute exposure scenarios are already developed. Examples are the acute reference dose for pesticides and the Dutch Intervention Levels for Hazardous Substances for emergency response planning. In case of accidental exposures there is often a need for a quantitative estimate of the risk for adverse effects rather than for a qualitative estimate (*i.e.* whether or not a standard is exceeded). The necessity of taking specific measures or precautions has to be evaluated for which a quantitative risk estimate is a prerequisite.

A specific toxicological endpoint that is often of great social relevance is carcinogenicity. The question arises whether a single (one-day) exposure to a chemical substance with a carcinogenic potential can give rise to tumour development and, if so, whether this risk can be quantitated. A specific approach is required, since most studies and risk assessments on carcinogenicity focus on lifetime daily exposure. A project was undertaken to study the possibilities to develop a specific decision tree for evaluation of the carcinogenic risk in case of acute exposure to potential carcinogens.

The present report describes some basic information used as starting point for the initial discussions. The background and results of these discussions are described in Chapter 2. These discussions led to a workshop for which interested parties, scientists as well as representatives from several governments, were invited. A report of this workshop is laid down in Chapter 3. A proposal for further elaboration of the risk assessment of peak exposure to carcinogenic substances, based on the findings of the workshop, is presented in Chapter 4.

2. Background information

The present project was not directly aimed to perform a detailed literature search and to provide a comprehensive overview of the subject. Basic information for the present project was obtained from the evaluation of Verhagen *et al.* published by the Health Council of the Netherlands (Health Council of the Netherlands, 1994). A fast screening of the recent literature did not reveal significant additional information. A recent analysis by Halmes *et al.* (2000), who compared the results of stopexposure experiments with lifetime carcinogenicity experiments for 11 substances, is summarised. The conclusions of these documents were discussed with dr. C.F. van Kreijl, dr. H.J. van Kranen, and dr. J. van Benthem (RIVM/TOX).

The report of the Health Council of the Netherlands
The report published by the Health Council of the Netherlands in 1994 addressed the cancer risk associated with peak exposure. Peak exposure was defined as a single instantaneous exposure lasting less than 24 hours to a high dose of a chemical. Their key question was: 'What is the estimated cancer risk of peak exposure to a genotoxic carcinogen *relative* to the cancer risk of the same total dose of this carcinogen distributed over an entire lifetime?' For this purpose a Dose-Rate Correction Factor (DRCF) was defined as 'a factor by which the tumour incidence caused by a specific dose of a chemical carcinogen at low dose rates is multiplied to derive the tumour incidence at high dose rates'. A quantitative estimate of the DRCF was strived at through a thorough evaluation of the literature. Both experimental studies and theoretical calculations were considered.

Evaluation of the limited human data and the experimental data with laboratory animals led to the conclusion that short-term or single exposure could give rise to additional tumour development.

Previous evaluations were summarised revealing a diversity of opinions. The USEPA (1986) assumed that the DRCF equals unity[1], whereas the Commission on Toxicology of the US National Research Council estimated a maximal value of 2.8 for the DRCF (COT, 1986) based on a theoretical approach by Crump and Howe (1984). ECETOC (1991) reported the probability of tumour development after a short accidental exposure to be extremely low. Illing (1989) recognised that a single exposure may lead to tumour development but considered it impossible to estimate the associated risk.

Two models used for a theoretical approach of the relative tumour risk after instantaneous exposure were described: the Armitage-Doll multi-stage model (AD-ms) (Crump and Howe,

[1] More recently, USEPA published a revision of these guidelines (USEPA, 1996) in which the following statement was made: 'The assumption was made that a high dose of a carcinogen received over a short period of time is equivalent to a corresponding low dose spread over time. While this is a reasonable default assumption based on theoretical considerations, departures from it are expected'. The cumulative dose may be replaced with other dose measures under the condition that 'the rationale for the selected approach is explained'.

1984) and one based upon the Moolgavkar-Venzon-Knudson 2-stage life-death model (MVK-2s) (Chen *et al.*, 1988). The AD-ms model is based on the assumption that neoplastic transformation requires three to six changes in the cellular genome. An assumption underlying the MVK-2s model is that two sequential changes in the cellular genome are required for malignant transformation. The first would be brought by an 'initiator' (transformation from a normal cell into an intermediate) and the second by a 'completer' (transformation of an intermediate cell into a malignant cell). Cell division and cell death are incorporated in the model.
Three categories of comparisons were made with these models, instantaneous high-dose versus long-term low-dose exposure, short-term low-dose versus long-term low-dose exposure, and studies on the effects of cessation of exposure. The first category is the most relevant one for the present discussion. Both the AD-ms and the MVK-2s model estimate that the highest risk is theoretically associated with a peak exposure in an early lifestage and involves a compound affecting an early stage of carcinogenesis. The opposite holds for carcinogens that will affect the last stage of carcinogenesis. The magnitude of the increased risk depends on the assumed number of stages in carcinogenesis (in the AD-ms model), the stage affected by the carcinogen, and the age at which instantaneous exposure occurs. For example, the risk for a young child acutely exposed to a late-stage carcinogen to develop a tumour at 70-years of age is zero, while a DRCF of 6 (AD-ms) or 7.1 (MVK-2s) can be estimated for exposure to an early-stage carcinogen during childhood. It was concluded that at worst, under the assumptions presented, the DRCF of peak exposure was 7.

Children may also be considered as a group at extra risk for biological reasons. In children, several tissues are in a stage of development showing a high level of cell proliferation and therefore, will be more susceptible to carcinogenic agents. Other biological processes like biotransformation and DNA-repair are not accounted for in the models. The AD-ms should correct for nonlinearity in the dose-response relation caused by *e.g.* nonlinearity in kinetics. Other assumptions made are that each step in the carcinogenic process is irreversible and that the different stages must occur in a specific order.

Seven experimental studies with animals were reported in which tumour incidence following a single exposure was compared with that following multiple exposures to the same cumulative dose (divided over 2-50 fractions). The DRCF ranged from 0 to 3.3 in 6 studies, but from 2.9 to 8.3 in one study (with methyl nitrosourea). No increased tumour incidence was observed in one additional inhalation study with mice receiving a single exposure to 1,3-butadiene (up to 10,000 ppm for 2 hours). A DRCF of up to 5.5 was calculated for an additional three studies in which animals received a similar total dose but for a shorter or longer time period.

A separate chapter discussed the use of data on kinetics, metabolism, and DNA-repair within the context of risk assessment of single exposure to carcinogens. A few examples (among others methylene chloride, benzene, vinyl chloride) were presented to illustrate how PBPK-

modelling could be helpful to identify the appropriate internal dose metrics and to estimate the biologically effective dose. It was concluded that saturation of metabolic processes and DNA-repair may crucially influence the DRCF for peak exposure to genotoxic agents. However, it was only generally concluded that the net effect of a high dose on the DRCF of peak exposures depends on the relative contributions of all the processes contributing to these protecting and toxifying factors. This is dependent on whether the processes involved inhibit or stimulate the processes of tumour induction.

Halmes et al. (2000)
This paper did not deal with peak exposures but focussed on the hypothesis that short-term exposure to carcinogens (stopexposure experiments) would lead to proportional decreases in cancer risk when compared to lifetime exposure. They retrieved 11 substances from the NTP-database for which the appropriate data were available; in total 59 tumour endpoints were studied. The exposure in the stopexposure experiments ranged from 13 to 66 weeks after which the animals were observed for their remaining lifespan. The hypothesis was tested using three different ways of statistical analyses.

1) The total dose in the stopexposure experiment was converted to a lifetime (2-year) average dose. It was then determined for each cancer endpoint whether the tumour response from the stopexposure experiments combined with the corresponding 2-year average doses fell on the dose-response line generated by continuous, lifetime exposure. It was found that for 6/11 substances the tumour response was higher in the stopexposure experiment as compared to lifetime exposure for at least one cancer endpoint. For two of these substances this was the case for all cancer endpoints. For several substances the cancer risk in the stopexposure experiment was sometimes higher and sometimes lower when compared to lifetime exposure, depending on the cancer endpoint. The response in the stopexposure experiments differed significantly from the response in lifetime exposure for 33/59 cancer endpoints.
2) The ED_{01} (the estimated dose yielding a 1% tumour response) estimated from the lifetime exposure dose-response line was compared with the ED_{01} calculated from the dose-response line based on the combination of the lifetime exposure data and the stopexposure data. These analyses could be performed for 47 cancer endpoints. The ED_{01} based on the combined data was lower for 37/47 cancer endpoints. For 24 endpoints the decrease was more than a factor of 2, and for nine endpoints even more than a factor of 10. Only for two endpoints the ED_{01} based on the combined data was increased by more than a factor of 2. These analyses showed that stopexposure experiments (short-term exposures) more often lead to a higher cancer risk than lifetime exposure to a similar cumulative dose.
3) The ‘equivalent averaging times’ (EAT) were calculated as follows. The response corresponding to the dose rate in the stopexposure experiment was estimated from the dose-response line from the lifetime exposure experiment. Next, the EAT was calculated from the dose-response data from the stopexposure experiment, *i.e.* the duration of

exposure necessary to reach the response estimated from the lifetime dose-response line. An EAT of 104 weeks meant that the response in the stopexposure experiment perfectly fitted on the lifetime dose-response line, whereas an EAT<104 weeks indicates a higher response than expected from the lifetime dose-response curve. The EAT was longer than the exposure duration in the stopexposure experiments but shorter than 104 weeks for most cancer endpoints, the median was 62 weeks. The EAT was even shorter than the exposure duration in the stopexposure experiment for incidental cancer endpoints.

The authors put forward some points for discussion although they considered the data too scarce for clear overall conclusions. Linear extrapolation from lifetime exposure experiments to a short-term exposure may lead to both an underestimation and overestimation of the cancer risk, but may result more often in an underestimation. Important is whether the short-term exposure will be during a specific life-stage during which the exposed subject is more susceptible to tumour formation. Further, organotropism was observed for two substances, *i.e.* tumours were observed in the stopexposure groups while no tumours were found in these sites after chronic exposure.

Discussion within RIVM
Participants were dr. C.F. van Kreijl, dr. H.J. van Kranen, and dr. J. van Benthem (RIVM/TOX) and dr. M.T.M. van Raaij and ir. P.M.J. Bos (RIVM/SIR). A brief overview of the relevant topics that were discussed is presented.

The distinction between ‘initiators’ and ‘promoters’ or ‘completers’ was considered to be difficult to make in practice. It may provide an oversimplified description of the complex carcinogenic process. Also the order of events in time will not be that specific, exposure to a ‘promoter’ may precede exposure to an ‘initiator’. A promoter may for instance, give rise to an increased cell proliferation rate and, hence, make the cell more susceptible to other promoters, thereby acting as an initiator. Finally, some substances may act both as a promoter and as an initiator.

Both the AD-ms and the MVK-2s model were considered to lack a clear biological basis. Not the number of stages will be of importance but rather the rate-limiting stage(s). The increased susceptibility at exposure in early life is not only for mathematical or statistical reasons, but also because children will have a relatively high cell proliferation rate in several tissues, depending on the stage of their physical and physiological development. Exposure to a genotoxic carcinogen during a stage of high cell proliferation may lead to an increased tumour response. It was proposed that individuals may be at higher risk when the tissue site that is the primary target for the regarding carcinogenic substance, shows a high cell proliferation rate. An example may be mammary tissue in female adolescents. This possibility may be further explored. However, the situation may be different for genotoxic and non-genotoxic carcinogens. It was suggested that exposure to genotoxic carcinogens might induce a higher risk at relatively early life stages (due to increased cell proliferation

rates) while exposure to non-genotoxic carcinogens might induce a higher risk at relatively late life stages (due to a diminished repair-capacity).

The concentration of the carcinogen in the target tissue was the preferred dose surrogate. PBPK-modelling could be a valuable tool to estimate the target tissue dose or concentration. The AUC might be the relevant dose metric for genotoxic agents, whereas for non-genotoxic carcinogens the maximal concentration might be the appropriate parameter.

Although the DNA-repair capacity might be exceeded at high exposure levels, the chances for apoptosis will also be increased. The net balance between these two phenomena cannot be estimated for the moment.

The neonatal mouse model was put forward as a study protocol of interest for peak exposures. Animals are exposed on only one or a few days, and might especially be suitable for the detection of genotoxic substances acting as an initiator. Disadvantages of this model are the route of administration (ip-injection is a less relevant route for risk assessment) and the fact that the target organs are generally limited to liver and lung. It will be difficult to use these data for the prediction of target tissues when exposed later in life and to estimate the carcinogenic risk quantitatively.

Additional considerations

A separate topic of discussion to be considered is the method of extrapolation to derive a quantitative risk estimate for peak exposure to carcinogens. Generally this is based on dose associated with a risk estimate for humans based on a chronic animal experiment. This human risk estimate (dose associated with an additional lifetime risk of *e.g.* 10^{-6}) is derived by linear extrapolation. The lowest dose in the animal experiment that is associated with an increased tumour incidence is extrapolated downwards over a large dose-range thereby introducing a number of, generally unknown, uncertainties. If the risk estimate for peak exposure is based on the human risk estimate for chronic exposure, the dose will be extrapolated upwards again and one somehow has to deal again with the same uncertainties. It has sometimes been stated that an estimation of the carcinogenic risk following a peak exposure based on a human carcinogenic risk estimate for chronic exposure is associated with too many uncertainties. However, these uncertainties may not be much different from those associated with the estimation of a human carcinogenic risk for lifetime exposure based an a chronic animal experiment. It may be worthwhile to study the possibilities for a direct exposure over time from chronic to acute exposure.

3. Workshop report

3.1 Starting points

A workshop was organised to discuss the (governmental) advisability and (scientific) possibilities to develop a decision tree for the evaluation of a single exposure to a carcinogenic substance. Single acute exposures to chemical substances will be relevant for several exposure situations: contamination of food and food products, short-term exceeding of environmental standard values due to environmental releases, accidental occupational exposures, and acute exposures during accidents. The workshop aimed at bringing together the policy points of view on this topic from several Ministries and the scientific standpoints. Representatives from the Ministries of Health, Welfare and Sports (VWS), of Housing, Spatial Planning and the Environment (VROM), of Social Affairs and Employment (SZW), of Agriculture, Nature managing and Fisheries (LNV), and of Transport, Public Works and Water Management (VenW), from the Health Council of the Netherlands, from TNO, and from the RIVM were invited. The program of the workshop is given in Appendix A and the list of participants in Appendix B (both in Dutch).

Preceding the Workshop the following questions were distributed to the participants.

1) Is carcinogenicity an important and relevant endpoint for human risk assessment following acute exposures?
2) Is it considered necessary and advisable to deviate from a general risk assessment procedure and to differentiate between substances in order to prevent over- or underestimation of the carcinogenic risk?
3) If differentiation is advised, is it then possible to develop a decision tree for substance-specific DRCF values to account for an increased or a decreased tumour risk after single exposure as compared to lifetime exposure? Differentiation could, for instance, be based on the target organ (*e.g.* increased risk when exposure occurs during a developmental phase of the organ accompanied by a high cell proliferation rate) or subpopulations at extra risk.
4) Extrapolation steps associated with risk assessment for single exposure differ from those for chronic exposure; the main step is extrapolation over time. Which aspects specific for this type of extrapolation can be identified and how can these aspects be dealt with? These aspects may include:
   a) Saturation of biotransformation processes;
   b) Saturation of DNA-repair mechanisms relative to the occurrence of apoptosis;
   c) The occurrence of organotropism.

Prior to the discussions four presentations were scheduled to indicate the points of departure with the following topics:

- Background and aim of the workshop.
- Starting points and overview of relevant topics.
- Policy viewpoints and needs (Ministries of Health, Welfare and Sports (VWS) and of Housing, Spatial Planning and the Environment (VROM)).
- (Im)possibilities of quantitative risk assessment of short-term exposure to carcinogens.

3.2 Presentations

Background and aim of the workshop

Incidental exposure to carcinogens can occur as a result of several events, *e.g.* contamination of foods, through industrial releases into the environment, and through releases in (occupational) accidents (at storage, processing or during transport). For some of these situations standards or guidance levels are being derived like the acute reference dose, AEGLs or ERPGs, 15-min TWA OELs, etc. One of the major issues in case of incidental exposure is the social concern for carcinogenic effects. The carcinogenic risk assessment after single accidental exposure is associated with many uncertainties. The question arises whether carcinogenicity is an appropriate endpoint for setting limit values for acute exposures. Aspects to be considered include, among others, the size of the exposed population and the carcinogenic risk relative to the risk for other noncarcinogenic effects. It was pointed out that the workshop should address the importance of assessing the carcinogenic risk after an acute exposure, the method of extrapolation from chronic to acute exposure, and the possibilities for the development of a decision tree.

Starting points and overview of relevant topics

A brief summary of the main conclusions from the report from the Health Council of the Netherlands was presented (see Chapter 2). The main question to be dealt with was 'What is the estimated cancer risk of peak exposure to a genotoxic carcinogen *relative* to the cancer risk of the same total dose of this carcinogen distributed over an entire lifetime?' This relative risk could be quantified by deriving a DRCF which can be defined in formula as:

$$DRCF = \frac{I_a}{I_c} \quad (\text{with } d_a * t_a = d_c * t_c).$$

In which:

I_a = tumour incidence after acute exposure,
I_c = tumour incidence after chronic exposure,
d_a = dose rate (daily dose) in acute exposure,
d_c = dose rate (daily dose) in chronic exposure,
t_a = exposure duration (days) in acute exposure,
t_c = exposure duration (days) in chronic exposure.

Quantification of a DRCF was intended to be the result of a decision tree made up of several decision steps. Possible factors that might be of interest are whether or not:

- an external peak exposure leads to an internal peak exposure in the target tissue (*e.g.* with the aid of PBPK-modelling),
- saturation of the biotransformation occurs (bioactivation or inactivation),
- saturation of repair mechanisms and apoptosis occurs,
- age(s) with an increased susceptibility can be discerned (*e.g.* stages of organ development attended by a high proliferation rate).

A separate point of discussion is the extrapolation of carcinogenic data obtained with chronic exposure experiments to an estimation of the human carcinogenic risk after acute exposure. Generally, in case of a risk assessment for an acute exposure to a carcinogenic substance, the exposure will be compared with a human limit value for carcinogenic effects based on lifetime daily exposure. In the Netherlands, this limit value is derived by linear extrapolation of a daily dose in a chronic animal experiment that is associated with a significantly increased tumour incidence to a human daily dose at which the additional carcinogenic incidence is considered negligible (usually 10^{-6}). The daily dose is extrapolated downward over several orders of magnitude and the extrapolation is associated with a number of uncertainties and (worst-case) assumptions. No interspecies extrapolation factor is applied. When the thus derived human limit value is subsequently extrapolated linearly over time to a one-day exposure the daily dose will be extrapolated upward over several orders of magnitude. The assumptions and uncertainties involved will at least partly be similar to those associated with the downwards extrapolation, and are then encountered (and accounted for) twice. This may unnecessarily increase the uncertainty in the final result. It may therefore, be worth the effort to study the possibilities for a direct extrapolation from a chronic animal experiment to a human carcinogenic risk after a one-day exposure. An initial attempt is given below.

The principal underlying basis is that the increased incidence observed in the (chronic) animal experiment (I_e) is linearly related to the cumulative dose, *i.e.* with $d_c * t_c$. The cumulative dose associated with a negligible additional tumour incidence for humans of, say 10^{-6}, following lifetime exposure to a carcinogen is then:

$$\frac{10^{-6}}{I_e} * d_c * t_c.$$

Subsequent extrapolation to a single, one-day (t_a) exposure, assuming a human lifetime of 25,600 days (approximately 70 years) results in:

$$25{,}600 * \frac{10^{-6}}{I_e} * d_c * t_a;$$

then $t_a = 1$, and the one-day dose $d_a = (25{,}600 * \frac{10^{-6}}{I_e} * d_c =) \frac{0.0256}{I_e} * d_c$.

Hence, if a dose rate d_c in the chronic experiment resulted in an observed increased risk (I_e) of 2.56%, d_a is equal to d_c. (Starting from higher observed tumour incidences, d_a will be proportionally lower). In that case the one-day dose-rate expected to result in an additional tumour incidence of 10^{-6} for humans is of the same order of magnitude as the dose-rate administered in the chronic animal experiment. Complex aspects as the dose-dependency of metabolic processes and repair mechanisms and the phenomenon of organotropism will then not be an important issue and will not have to be accounted for. A direct extrapolation of the tumour incidence over time, *i.e.* a direct extrapolation from a chronic exposure study to a one-day exposure, may therefore be associated with less uncertainties than extrapolation via a human limit value for lifetime exposure.

Policy viewpoints and needs (Ministries of Health, Welfare and Sports (VWS) and of Housing, Spatial Planning and the Environment (VROM))
The Ministry of VWS highlighted a few matters of policy for which risk assessment of peak exposure to carcinogenic substances is of importance: food safety, consumer safety, in case of emergencies, and transportation. In case of an incident the steps to be followed include the evaluation of whether a public health risk is present, a rough estimation of the risk, taking of appropriate measures (recall, information to the public), and informing concerned parties (Minister, the Lower House, Consumer organisations).

The risk assessment is usually based on standards for chronic exposures. Questions of importance for policy making are whether a single exposure can lead to tumours, what mechanistic data are available, how is the carcinogenic risk related to noncarcinogenic effects (also considering risk perception), and can subpopulations at increased risk be identified? Especially children should be considered as group at extra risk because of a high level of organ development and, therefore, a high rate of cell proliferation, and because children have a relatively high food intake per kg bodyweight.

The Ministry of VROM addressed the significance of risk assessment of peak exposure to carcinogens to draw up contingency plans. These plans should not only focus on acute effects but also on chronic effects following a single exposure. Carcinogenicity is at present not an issue for External Safety. It was asked whether this was considered to be justified. Attention was drawn to the conclusion of the report of the Health Council of the Netherlands that peak exposures also could lead to a shortening of the latency time, which should also be subject of the risk assessment process. A proper cost-benefit analysis was deemed of importance to consider whether the benefits of the development of an appropriate tool, for instance a decision tree, will counterbalance the costs.

(Im)possibilities of quantitative risk assessment of short-term exposure to carcinogens
The conclusions of the report of the Health Council of the Netherlands were summarised in which a default value of 10 for the DRCF was proposed. Several uncertainties are involved in the derivation of a DRCF. The DRCF depends on whether the carcinogen should be considered an initiator or promoter, on the age of the exposed individual at the time of exposure, on metabolic processes, and on DNA-repair mechanisms. A distinction was made between carcinogens with and without a threshold value below which the carcinogenic risk would be zero. The carcinogenic risk was estimated to be zero for threshold carcinogens as long as a short-term exposure would be at or below the NOAEL for acute or subacute exposures. An increased carcinogenic risk is expected at exposure levels above this threshold, with an increasing risk in case of higher, longer, or more frequent peak exposures.

Information about tumour type and site, the dose-response relation, kinetic data, the mechanism of action, and whether or not the cumulative dose is of importance, could provide valuable information for a quantitative risk assessment for single exposure to carcinogens. Further, the acute toxicity should be carefully considered as well. For a proper evaluation the Benchmark approach might be a more valuable tool for the present purpose than linear extrapolation.

It was concluded that evaluation of the carcinogenic risk of a short-term exposure to a carcinogen would be relevant, both for threshold and non-threshold carcinogens. The DRCF may be a valuable tool for this purpose, but a default factor of 10 is yet insufficiently founded. The development of a decision tree should be welcomed but the practical use of such a tool should preferably be in the hands of a group of experts.

3.3 Discussion

After the presentations, the workshop proceeded with group discussions followed by a plenary discussion. The basis for these discussions were the four questions presented in section 3.1. These topics were thoroughly discussed and led to a number of suggestions and possibilities that could be worked out into more detail in the future. Due to the complexity of the subject clear answers were not to be expected beforehand. The present section presents an overview of the discussions and the proposed suggestions.

Carcinogenicity was considered to be a relevant endpoint for risk evaluation following peak exposure both from a scientific as well as from a policy point of view. It was remarked that the interest in the endpoint of carcinogenicity is often driven by social concern. It may sometimes be more a problem of risk perception rather than the actual presence of a carcinogenic risk. Hence, a good communication to the general public is important, especially when the carcinogenic risk is estimated to be of negligible concern.

Attention should first be given to the definition of acute or peak exposure. Peak exposure was initially presented as a one-day exposure. Different definitions appeared to be operable between the Departments. Depending on the type and circumstances of an accidental exposure (*e.g.* accident during transportation, industrial accident, contamination of food) the exposure duration may last from a few minutes to several days. Therefore, some participants felt more comfortable to define the duration of a single exposure in coherence to the duration of an event. A peak exposure can then include a few days of exposure (*e.g.* in case of contamination of food products) or even a few weeks in the situation that a contamination is not rapidly recognised.

The development of a decision tree was endorsed, it will provide guidance to consider all the relevant elements involved. The subject was considered to be very complex in the sense that it would be difficult to set up such a decision tree and to identify and develop the appropriate criteria. A tiered approach was suggested with a first rough estimate of the risk through linear extrapolation and a DRCF of *e.g.*10, to start with. The outcome can be compared with the risk for acute non-carcinogenic effects, analogous to the procedure for the derivation of Intervention Levels for Hazardous Substances for emergency response planning. The Ministry of VROM strongly suggested that a decision tree should be gradually developed in order to avoid a too much detailed (and costly) but less workable tool. The Ministry of VenW addressed the necessity to develop such a tool within an international framework to facilitate international acceptance which is for instance of importance for international transport of chemical substances.

Another proposal was a categorical decision tree, by which carcinogens could be divided into categories by *e.g.* structural alerts and using weighing factors. This proposal was generally considered to hold prospects that need further exploration. A categorical decision tree easily offers the possibility for a differentiation of carcinogenic substances and classify them into different categories, but it will require a multidisciplinary approach. The aspect of differentiation needs further elaboration, it may be a difficult task which will often not be possible but may also not always be necessary. For instance, a chronic animal experiment covers exposure over almost the entire life span (with exception of the first few weeks). It may therefore, provide a conservative estimate for short-term exposures during a shorter period of time, especially if d_a is more or less equal to d_c (see section 3.2). The chronic study may then be regarded as the sum of all possible individual one-day exposures during an entire life. All life stages during which an individual is at higher risk are then covered by the chronic experiment.

In summary, risk assessment of peak exposure to carcinogenic substances is an important topic which should be elaborated. Since the subject is very complex, a gradual development of a (categorical) decision tree was proposed with the remark that each step should be carefully evaluated in order to come up with a workable scheme. It was welcomed to work out additional guidance to differentiate between carcinogens but no additional criteria for

differentiation, other than already mentioned, were brought forward. Further exploration of the possibilities for an appropriate method for extrapolation over time was considered to be meaningful.

4. Research proposal

The discussions and suggestions of the workshop showed that both policy makers and scientists considered carcinogenicity as an important endpoint for the risk assessment of peak exposures. The development of a decision tree was endorsed although it was recognised to be a difficult task due to the complexity of the subject. For this purpose, a multidisciplinary working group of experts will be established. Experts from different institutes (RIVM, TNO) will be asked to join. A draft proposal will be presented to a few additional experts in the field of carcinogenic risk assessment for comments. The working group will address the following issues.

At first a feasible definition of peak exposure is needed. It should be studied from the viewpoint of risk assessment whether it is necessary to distinguish between a one-day exposure and daily exposure for a few weeks.

A first onset for a decision tree may be a rough layout that could be further refined by ongoing experience and be validated by model-substances. Experience will not only provide better insight in the possibilities but also in the gaps in knowledge and may give specific guidance to the direction of further research. It was suggested that validation may also occur through experiments with transgenic mice. Elements that should be considered as part of the decision process were mechanism of action and of DNA-repair.

A tiered approach is recommended for the decision tree because it is to be expected that for many substances only a limited amount of data will be available. It is therefore, advisable to incorporate a first tier to limit the number of carcinogens. For the same reason of limited data availability, the decision tree will probably lead to a semiquantitative risk assessment, *i.e.* lead to a categorical division of carcinogenic substances. It will be studied which categories will be the most appropriate and the criteria to distinguish between these categories of carcinogens will be identified and further developed.

The basis for risk assessment of exposure to carcinogenic substances will generally be a chronic animal experiment, this will also be the case for risk assessment of acute exposures. As discussed in Chapter 3, the suitability of the concept of cumulative dose when extrapolating from chronic to a one-day exposure may be questionable for several reasons. It will be studied how the uncertainties involved can be dealt with and whether they can be quantified if necessary. It will be kept in mind that although the risk assessment for chronic exposure to carcinogens is also associated with a number of (not quantifiable) uncertainties, the method is considered workable for human risk assessment. Reasoning analogously, the working group will not strive to provide proper answers to all questions that will arise or account for all uncertainties involved but will focus on the development of a workable decision tree that will be straightforward and transparent.

The method of extrapolation over time from chronic to acute exposure also requires further elaboration. An important topic will be the significance of age at exposure. Although the theoretical models appear to lack a clear biological basis it may be useful to study the possibilities of these models for extrapolation over time into more detail. Even if they provide a simplified description, they may still be more accurate than the presently used methods for risk assessment for acute exposures or may provide some guidance to the process.

A few additional aspects regarding the extrapolation over time and the derivation of DRCFs need further attention before a decision tree can be developed. In most carcinogenicity studies with short-term exposure (*e.g.* one-day exposure or stopexposure) animals are exposed at a relatively young age, when they may be relatively more susceptible to carcinogens. Comparison of the dose-response relation of these short-term experiments with those obtained with chronic experiments may then lead to an overestimation of a population-based carcinogenic risk after a short-term exposure. (It is noted that these short-term experiments may be suitable to estimate the carcinogenic risk for a subpopulation of young people). Animal experiments with a short-term exposure to carcinogens at different life stages will be valuable to study this aspect. These kind of studies have been performed with for instance methylene chloride (Kari *et al.*, 1993) and vinyl chloride (Drew *et al.*, 1983). On the other hand, the time at which a tumour becomes manifest in a chronic experiment is of importance. The tumour incidence is then related to the cumulative dose administered over the entire exposure period. It may however, be more accurate to use only the cumulative dose up to the time that a tumour becomes manifest. By adding the administered dose after this time point to the cumulative dose the carcinogenic potency of long-term exposure will be underestimated. The overall result of overestimating the carcinogenic potency of short-term exposure in combination with an underestimate of the long-term carcinogenic potency may result in an overly conservative estimate of the carcinogenic risk of peak exposures in humans thus of the DRCF. This should be further explored.

In conclusion, the principal aim of the working group will be the development of a straightforward (categorical) and transparent decision tree. A first tier will be incorporated to serve as a filter in order to limit the number of carcinogens to be classified. The criteria for the division in categories, *i.e.* to differentiate between carcinogens, will be further developed, a few possibilities are already mentioned. Possibilities for additional criteria will be explored. The validity of the basic concept of tumour incidence being related to the cumulative dose will be verified for acute exposures. The extrapolation over time from chronic to acute exposure, and how this can be incorporated in a decision tree will be addressed. The decision tree will be validated by model-substances. A draft proposal will be send for comments to additional experts.

References

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Appendix 1 Workshop program

Workshop Risicobeoordeling piekblootstelling aan carcinogene stoffen

Doelstelling: Ontwikkelen van een beslisboom voor een kwantitatieve risicobeoordeling bij een kortdurende blootstelling aan carcinogene stoffen

Datum: 26 juni 2002
Tijd: 13.00 – 17.00 uur
Lokatie: Congreszaal VE 1.05
RIVM, Bilthoven

Voorzitter: T.G. Vermeire

Programma:

13.00 Ontvangst

13.10 Opening
T.G. Vermeire
13.15 Inleiding
M.T.M. van Raaij
13.25 Uitgangspunten en overzicht van relevante onderwerpen
P.M.J. Bos
13.40 Visie en wensen vanuit het beleid - Ministerie van VWS
J.M. de Stoppelaar
13.55 Visie en wensen vanuit het beleid - Ministerie van VROM
J. van Zorge
14.10 (On)mogelijkheden van kwantitatieve risicobeoordeling van kortdurende blootstelling aan carcinogene stoffen
V.J. Feron
14.30 Pauze

14.45 Groepsdiscussie
Discussie in twee groepen op basis van geselecteerde onderwerpen
16.00 Presentatie van de groepsdiscussies
Groepsvoorzitters/rapporteurs
16.20 Plenaire discussie
T.G. Vermeire
16.50 Samenvatting en conclusies
M.T.M. van Raaij
17.00 Sluiting
T.G. Vermeire

Appendix 2 List of Workshop invitees

Lijst van genodigden Workshop d.d. 26.06.02

1.		A.J. Baars	RIVM
2.		P.M.J. Bos	RIVM
3.		W.H. Könemann	RIVM
4.		F.X.R. van Leeuwen	RIVM
5.		M.T.M. van Raaij	RIVM
6.		T.G. Vermeire	RIVM
7.		M.W.M.M. Ruijten	RIVM
8.		J. van Benthem	RIVM
9.		H.J. van Kranen	RIVM
10.		C.F. van Kreyl	RIVM
11.		P.W. Wester	RIVM
12.	mw.	A.J.A.M. Sips	RIVM
13.		J.C.H. van Eijkeren	RIVM
14.		M.J. Zeilmaker	RIVM
15.		C. de Heer	TNO Voeding
16.		V.J. Feron	TNO Voeding
17.		E.D. Kroese	TNO Voeding
18.	mw.	P.W. van Vliet	Gezondheidsraad
19.	mw.	S.M. Potting	Ministerie VWS
20.		H. Roelfzema	Ministerie VWS
21.	mw.	J.M. de Stoppelaar	Ministerie VWS
22.		T. Blom	Ministerie VROM
23.		C. van den Boogaard	Ministerie VROM
24.		L.A.C. de Bruijn	Ministerie VROM
25.		J. van Zorge	Ministerie VROM
26.	mw.	A. Bongers	Ministerie SZW
27.		R.M.C. Theelen	Ministerie LNV
28.	mw.	H. de Wijs	Ministerie V&W
29.	mw.	T.F.M. Woeltjes	Ministerie V&W

Appendix 3 Mailing list

1-5. Directeur-Generaal van de Volksgezondheid
6. Dr. J.M. de Stoppelaar, Ministerie van VWS
7. Voorzitter van de Gezondheidsraad, Rijswijk.
8. Directie RIVM
9. Prof. dr. ir. D. Kromhout, sector directeur VCV, RIVM
10. Dr. C. de Heer, TNO Voeding, Zeist
11. Dr. E.D. Kroese, TNO Voeding, Zeist
12. Prof. dr. V.J. Feron, TNO Voeding, Zeist
13. Dr. P.W. van Vliet, Gezondheidsraad, Rijswijk
14. Dr. S.M. Potting, Ministerie van VWS
15. Dr. H. Roelfzema, Ministerie van VWS
16. Dr. C. van den Bogaard, Ministerie van VROM
17. Dr. L.A.C. de Bruijn, Ministerie van VROM
18. Dr. J. van Zorge, Ministerie van VROM
19. Dr. R.O.M. van Loo, Ministerie van VROM
20. Dr. T. Blom, Ministerie van VROM
21. Dr. A. Bongers, Ministerie van SZW
22. Dr. E. vd Stegen, Ministerie van SZW
23. Dr. R.M.C. Theelen, Ministerie van LNV
24. Dr. H. de Wijs, Ministerie van V&W
25. Drs. T.F.M. Woeltjes, Ministerie van V&W
26. Dr. A.J. Baars, SIR-RIVM
27. Drs. A.G.A.C. Knaap, SIR-RIVM
28. Drs. J.C.H. van Eijkeren, SIR-RIVM
29. Dr. F.X.R. van Leeuwen, SIR-RIVM
30. Dr. ir. M.N. Pieters, SIR-RIVM
31. Dr. A.J.A.M. Sips, SIR-RIVM
32. Dr. ir. M.J. Zeilmaker, SIR-RIVM
33. Dr. ir. M.W.M.M. Ruijten, LBM-RIVM
34. Dr. W.H. Könemann, CSR-RIVM
35. Drs. T.G. Vermeire, CSR-RIVM
36. Dr. J. van Benthem, TOX-RIVM
37. Dr. ing. H.J. van Kranen, TOX-RIVM
38. C.F. van Kreyl, TOX-RIVM
39. Dr. P.W. Wester, TOX-RIVM
40. Dr. R. van Gorcum, RIKILT, Wageningen
41. Depot Nederlandse Publikaties en Nederlandse Bibliografie, Den Haag
42. SBC/Communicatie

43. Bureau Rapportenregistratie
44. Bibliotheek RIVM
45-54. Bureau Rapportenbeheer
55-56. Auteurs
57-60. Reserve-exemplaren