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Review:

A concept for maximum exposure levels in cars

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ABSTRACT

Emission of volatile organic substances (VOC) from articles inside a car may lead to adverse health effects in exposed drivers. Presently, no general concept to derive maximum exposure levels inside cars has been published. Therefore, we recommend techniques for three types of maximum exposure levels inside cars, namely for (i) chronic exposure to non-genotoxic substances (ELIA, chronic), (ii) short term exposure inside automotive vehicles (STELIA) and (iii) genotoxic substances acting by threshold mechanisms (ELIA, cm). For derivation of the ELIA, chronic, we recommend to start with a *Lowest Observed Adverse Effect Level* (LOEL) or a *Benchmark Dose 10* (BMD_{10}) and use a procedure including four steps: a. estimation of the *No Observed Effect Level* (NOEL), b. extrapolation from laboratory animal to man, c. extrapolation to the general population due to interindividual differences and d. extrapolation to continuous exposure. To derive STELIAs a three-step-procedure is recommended, starting with a LOEL and a. estimating the NOEL, b. extrapolating from animal to man and c. extrapolating to the general population. Derivation of ELIA, cm, the maximum exposure level for carcinogens acting by a threshold mechanism, is certainly the most problematic procedure. We recommend to start with the lower 95% confidence limit for the most sensitive tumor type known in animals (BMD_{05}) and a. extrapolate from animal to man and b. use a safety factor of 1/50 000 unless specific research succeeded in demonstrating specific levels of thresholds. It must be considered that a general concept for maximum exposure levels can not replace an intelligent toxicological approach considering the mechanism of action of individual substances. However, the strategy suggested here offers a practical technique for identification of individual problematic exposures that require an intensive toxicological evaluation.

Keywords: Indoor air, emissions, exposure limits in cars, automotive vehicles, safety factors

INTRODUCTION

Indoor Air qualitity is of increasing interest for manufacturers, consumers and regulators. Catchphrases like *Sick Building Syndrom* or *Building Related Illness* draw a link between adverse health effects of residents to the quality of indoor air (Wiesmueller, 1997). One parameter between others that has an impact on indoor air quality is the emission of volatile organic substances from articles used in the indoor environment. The issue was picked up by regulators, and the *Construction Products Directive* of the

European Union (directive 93/68/EC) requires that construction products must not affect the health of residents.

If epidemiological and/or toxicological data for individual substances are available, they most likely represent workplace conditions. The deviation of *Workplace Exposure Limits* is well established. However, in indoor environments not only healthy workers are exposed, but also old and young people, children and sick people. The indoor air hygiene commission of the *German Environmental Protection Agency* ("Umweltbundesamt", UBA) published a scheme to derive *Target Recommended Maximum Exposure Levels* for indoor air (Innenraumlufthygienekommission des Umweltbundesamtes 1996). Safety-factors applied on NOAELs for individual compounds are applied to pay attention to extended exposure times and a more sensitive population. By this way, recommended *Maximum Exposure Levels* ("Richtwerte", RW) are derived which are applicable for indoor air in buildings.

The indoor air quality in cars also attracted the attention of scientists. For instance increased levels of DNA single strand breaks have been observed in mononuclear blood cells of taxi drivers (Oesch et al., 1994). Nearly all car manufacturers have individual lists or mutual lists of restricted substances. The aim of such lists is to avoid allegations due to smell and toxic effects caused by emissions from articles used inside the car. In the present article, we present a technique to derive *Maximum Exposure Levels* inside a car for chronic and short term exposures.

PROPOSAL FOR THE DERIVATION OF EXPOSURE LIMITS IN AUTOMOTIVE VEHICLES

In many instances driving a car is a workplace, e. g. for taxi-, bus- and lorry-drivers. In this respect, occupational exposure limits and maximum exposure limits applicable for workplaces may be used without any modification. However, at a workplace it is usually known what substances are handled and, therefore, which exposure limits have to be checked. This is different in a car, and it is prudent to check articles used inside the car in climate chambers in advance. Further, also children, elderly and sick people travel by car, so the higher sensitivity of the potentially exposed population has to be taken into account. It is to be expected that these sensitive individuals spend less than 40 hours per week in a car, as is the case for professional drivers. Nevertheless, an exposure-time adjustment seems to be justified as in some countries people spend more than 90 % of time in confined spaces, i.e. in flats and cars. Thus, there is no reason why people sitting in cars should be exposed to higher VOC concentrations compared to indoor air in buildings.

EXPOSURE LEVEL INSIDE AUTOMOTIVE VEHICLES (ELIA, CHRONIC)

To derive an *Exposure Level Inside Automotive Vehicles* (ELIA) for chronic exposure we recommend a procedure including four steps (a-d in Figure 1).

a. From LOEL to NOEL or BMD_{10}

The first step in the recommended procedure is derivation of the NOAEL or a benchmark dose 10 (BMD_{10}) (Crump, 1984) for non-genotoxic effects. Kalberlah et al. issued a report which provides guidance how and when the benchmark dose concept shall be used instead of the NOAEL (Kalberlah, 2003). For the next steps, the recommend-dations from ECETOC should be applied (ECETOC, 2003). The NOAEL may be estimated by dividing the LOAEL by a factor of three. The factor for the extrapolation from a LOAEL to a NOAEL depends on the quality of effects seen at the LOAEL and on the steepness of the dose-response curve. Lower or higher factors than three may be justified. If no data for chronic exposure are available, a divisor of six for sub acute data and a divisor of two for sub chronic data are used to estimate the NOAEL (chronic). For exclusively local effects below the level of

exposures causing systemic cytotoxicity, a duration extrapolation is not seen as necessary (ECETOC, 2003).

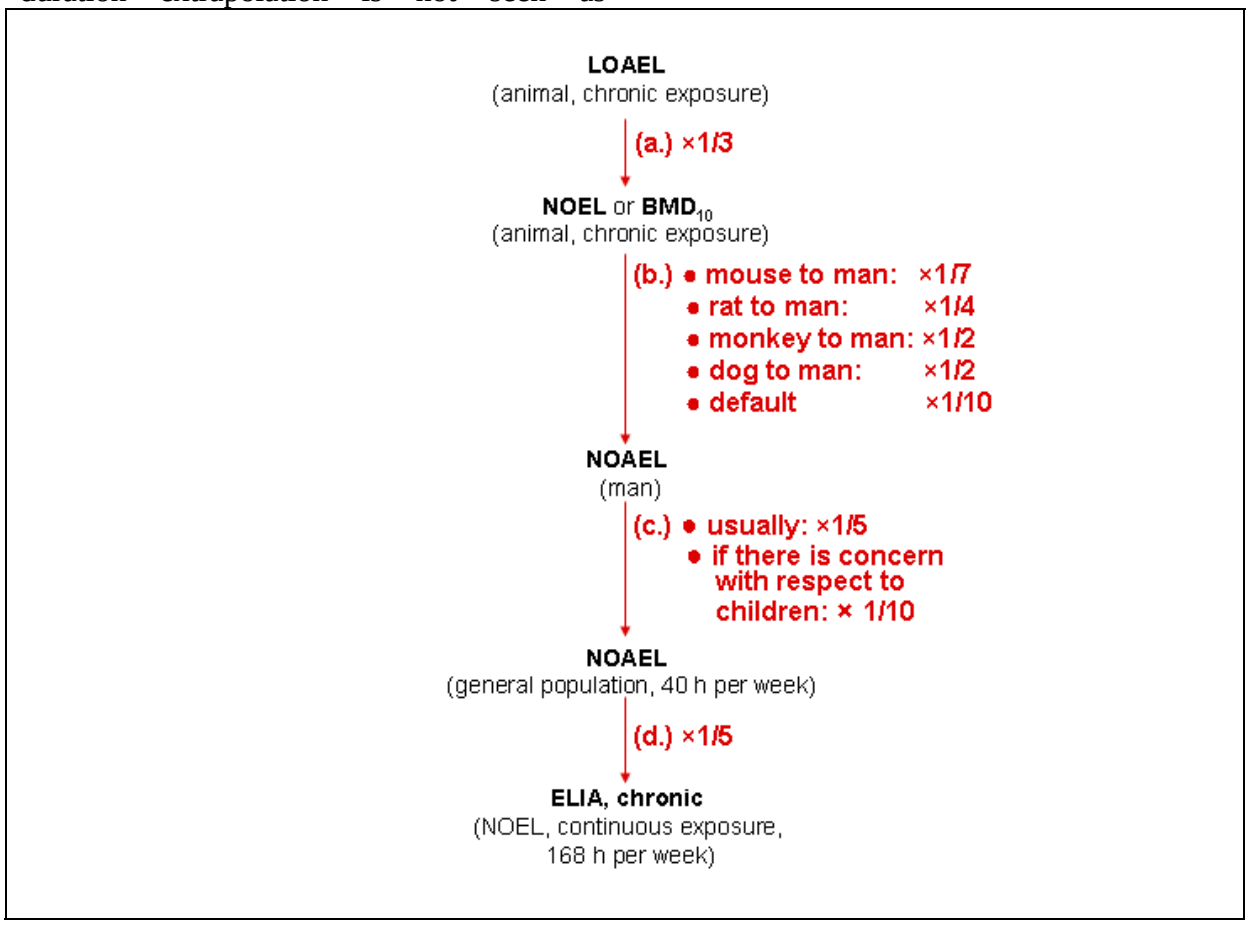

Fig. 1: Strategy to derive an *Exposure level Inside Automotive Vehicles* (ELIA, chronic) including four steps: a. estimation of the *No Observed Effect Level* (NOEL) from the *Lowest Observed Adverse Effect Level* (LOAEL), b. extrapolation from laboratory animal to man, c. extrapolation to the general population due to interindividual differences, d. extrapolation to continuous exposure with 168 h per week.

b. Interspecies extrapolation

Interspecies extrapolation can be done by scaling factors. A factor of seven for mouse to man, four for rat to man, two for monkey to man and two for dog to man has been recommended (ECETOC, 2003). Known differences in the metabolism may allow to modify these scaling factors. For local effects of water-soluble gases an extrapolation from animal to man is not necessary. The scaling factor may be adjusted if required by known differences concerning metabolism and toxicokinetics between animal and man. If there is reason for concern that an extrapolation by scaling might underestimate the risk for man, a default value of 10 may be used, as is done in the RW-concept of the German UBA (Innenraumlufthygiene-kommission des Umweltbundesamtes, 1996).

c. Interindividual differences

An intra species extrapolation-factor of five can be considered to be sufficient for the general population (ECETOC, 2003). The need for an additional factor for children is questionable if the substance is unlikely to affect the developing foetus. If there is reason for concern that children are not sufficiently covered, an additional factor of 2 may be introduced as is done in the RW-concept of the German UBA (Innenraumlufthygienekommission des Umweltbundesamtes, 1996).

d. Extrapolation to continuous exposure
As people in indoor environments may be exposed 168 h per week instead of only 40 h, a factor of 5 should be applied for the correction of exposure time for systemic effects. This factor might not be necessary for substances with a short half-life-time at concentrations below the NOAEL. Of main interest are effects provoked by inhalative exposure. Route to route extrapolation is strictly only feasible for systemic effects and provided data on toxicokinetic and metabolism are available. Unfortunately, this is frequently not the case for many substances relevant for indoor air. Oral to inhalative exposure extrapolation is critical, and the knowledge is limited. Some aspects to be taken into account are summarized by Schneider et al. (2003). The authors describe that there is a certain likeliehood to underestimate the risk. Work is cited which showed that the $NOAEL_{oral}$ needs to be divided by a factor of 1 to 200 to derive a correct $NOAEL_{inhal.}$. However, the database covering 28 substances was limited. As a pragmatic way forward, a one to one extrapolation from oral to inhalative exposure has been recommended, if there are no contradictive data (Technische Regeln fuer Gefahrstoffe 901, 2001).

SHORT TERM EXPOSURE LEVELS INSIDE AUTOMOTIVE VEHICLES (STELIA)

Especially at high temperatures some articles inside automotive vehicles may emit certain VOCs only for a short period of time. As a car may be heated up to 65 °C while parking in the sun in summertime, relatively high concentrations of irritative compounds or compounds acting on the central nervous system may result. Although the concentrations of VOC's slump down within 5 minutes after starting to drive, they may nevertheless be relevant (Bauhof, 1994). An adverse influence on the capability to drive a car cannot be excluded, as short term exposure to irritating substances may impair the vision of the driver, and his attention may be depressed by narcotic VOCs. Hence, it makes sense to derive *Short Term Exposure Levels Inside Automotive Vehicles* (STELIA) for irritating and narcotic properties of VOC's. We recommend a technique including three steps:

a. From LOEL to NOEL
Similarly as described for the derivation of ELIAs a factor of three is recommended to extrapolate from LOEL (animal) to NOEL (animal). Of course this extrapolation is not needed if a NOEL for acute exposure is already known. As outlined for the derivation of ELIAs, the extrapolation from a LOAEL to a NOAEL depends on the severeness of the effects observed at the LOAEL and the slope of the dose-response curve.

b. Interspecies extrapolation
Usually interspecies differences for acute toxic effects are smaller compared to chonic toxicity (Hengstler et al., 1998). Therefore, we recommend a less complex procedure compared to derivation of ELIAs. For symptoms of local irritation an extrapolation usually is not necessary resulting in a factor of one. For other types of acute toxicity a factor of 1/3 is recommended.

c. Interindividual differences
Similar as recommended for ELIAs an intra species extrapolation-factor of five is recommended. Since the STELIA has been constructed to assess short term exposures a further factor for exposure-time adjustment, such as 1/5 to extrapolate the ELIA, is not needed.

Respiratory sensitizers require a specific evaluation and are not covered here. The problem is a lack of commonly accepted animal models for the ranking and quantification of the potency of respiratory sensitizers.

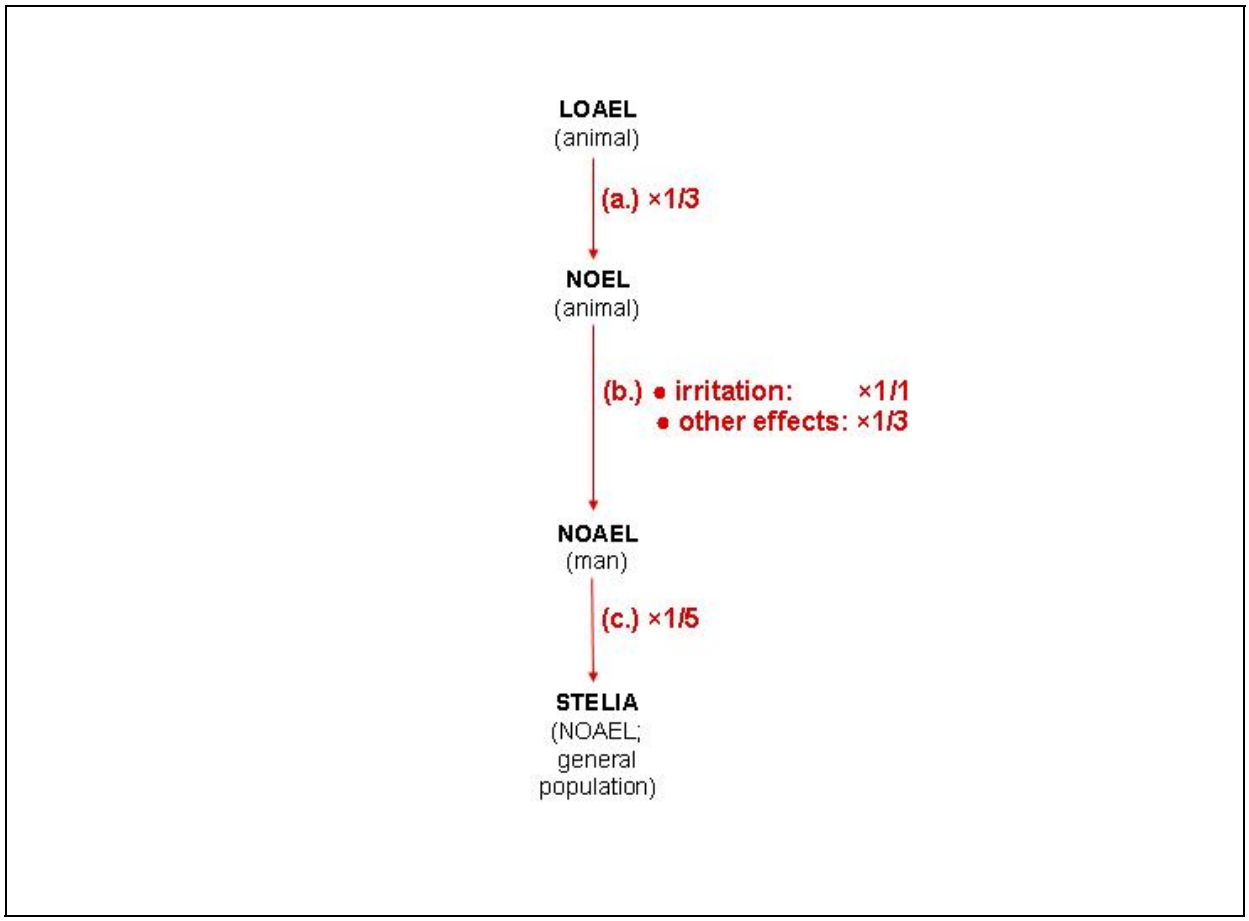

Fig. 2: Strategy to derive a *Short Term Exposure Level Inside Automotive Vehicles* (STELIA) including four steps: a. estimation of the *No Observed Effect Level* (NOEL) from the *Lowest Observed Adverse Effect Level* (LOAEL), b. extrapolation from laboratory animal to man, c. extrapolation to the general population due to interindividual differences.

GENOTOXIC SUBSTANCES (ELIA, cm)

It is common understanding that carcinogenic and mutagenic substances or substances toxic to reproduction of category 1 and 2 must not be used as additives for products intended for consumer use. However, such substances may be present as impurities or degradation products. The latter substances are considered as a severe problem if they are carcinogens without a known threshold mechanism (Streffer et al., 2004; Hengstler et al., 2003a; Arand et al., 2003). In this case large efforts are justified to avoid exposure to these carcinogens. For carcinogens that act by a threshold mechanism the situation is different. In some cases a total ban may be not necessary. Therefore, there is a need for *ELIAs for Carcinogenic and Mutagenic Substances*, ELIA(cm) acting by threshold mechanisms. Substances toxic to reproduction act either via non-genotoxic or genotoxic mechanisms. In the first case they are sufficiently covered by the ELIA (chronic), respecting available data on toxicity to reproduction. In the second case, the ELIA(cm) can be applied, if a threshold mechanism is known. We recommend a procedure including two steps:

a. Interspecies extrapolation
BMD_{05}, the lower 95 % confidence limit for the most sensitive tumor type observed in laboratory animals, may be used to derive an ELIA(cm). For interspecies extrapolation a similar technique as described for the ELIA (chronic) may be used.

b. Extrapolation from BMD_{05} (man) to ELIA(cm)
Derivation of "acceptable" exposures to carcinogens is always problematic, even if

threshold mechanisms have been demonstrated. Therefore, our presentation of a specific technique should be considered as contribution to a controversial discussion (Hengstler et al., 2003a; Streffer et al., 2004). Nevertheless, we believe that it is better to recommend a specific technique also for this problematic type of extrapolation. It should be considered that the present concept does not substitute for a scientific evaluation of individual carcinogens. However, our concept may help to identify problematic exposures that require further evaluation.

Establishment of an ELIA(cm) may be facilitated by physiologically based pharmacokinetic models (PBPK). In the case of vinyl acetate a PBPK model has been suggested to derive a threshold exposure (Figure 4; Hengstler et al., 2003a). There will be no carcinogenic effects if individuals are exposed to concentrations below this threshold level. It may be discussed controversially, whether the data are sufficient to justify the proposed threshold of 50 ppm vinyl acetate (Fig. 4), but the demonstrated general principle to define thresholds for substances that require toxicity for carcinogenic action should be acceptable.

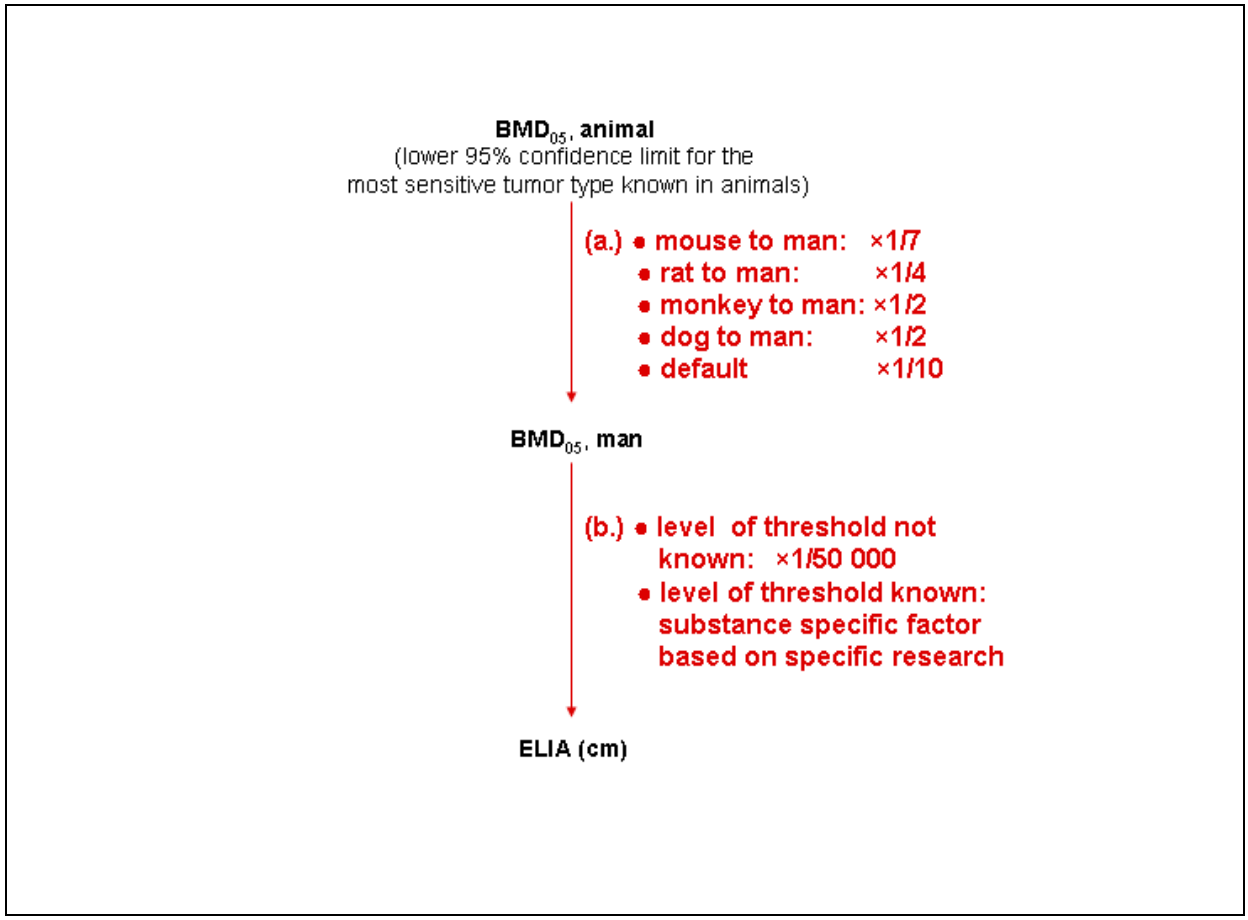

Fig. 3: Strategy to derive an *Exposure Level Inside Automotive Vehicles* (ELIA, cm) for carcinogens acting by a threshold mechanism. The suggested technique includes two steps: a. interspecies extrapolation to the human BMD_{05}, b. estimation of the ELIA, cm, using an uncertainty factor or by specific research that demonstrates threshold doses.

The situation is even the more problematic if mechanistic studies have shown the existence of threshold mechanisms, but no data are available defining the level of the threshold in human tissues. In this case we recommend a conservative procedure, introducing a factor of 1/50 000 to extrapolate from the BMD_{05} to ELIA(cm). The idea behind this

factor of 1/50 000 is that even under the very unlikely most pessimistic assumptions that (i) the threshold for carcinogenicity is below the ELIA(cm) and (ii) the dose-response curve for carcinogenicity is linear the additional risk over lifetime exposure is smaller than one in a million of exposed individuals (Diehl, 2003). This pessimistic assumption will usually result in ELIAs(cm) that are smaller than the threshold of a substance. We suggest application of this conservative procedure unless research allows a more precise definition of thresholds. If a BMD_{05} is not available the ELIA(cm) may also be based on the T25-concept. In this case a scaling factor has to be applied to extrapolate from animal to man, and a divisor of 250 000 is needed to come down to a lifetime risk of smaller than one in a million of exposed individuals.

PROBLEM OF SYNERGISM

Articles used inside cars usually emit many different VOCs. This fact leads to the question whether these substances may act synergistic, additive or antagonistic. The question of interference between different toxicants is a fundamental one in toxicology (Jung et al., 2003; Hengstler et al., 2002; 2003a,b; von Mach et al., 2002). For trace compounds below their individual threshold of action it is generally accepted that their action is additive. As an example, see the *Technical Rules for Handling Dangerous Substances* No. 403 in Germany (Technische Regeln fuer Gefahrstoffe 403, 1989), or the concept of *"Lowest Concentration of Interest (LCI)"* for VOC-emissions of construction products (AgBB, 2002). In this concept, a limit for total VOC of 1 – 3 mg/m³ is set to address possible synergistic effects of indoor air contaminants. It is recommended to make use of this approach also for the evaluation of the air quality inside cars. That means,

$$\mathbf{\Sigma(C_i/ELIA_i) \leq 1}, \qquad (1)$$

and

TVOC ≤ 3 mg/m³ (TVOC: total VOC),

where $ELIA_i$ and C_i are the exposure limits in automotive vehicles respectively the concentrations of individual VOCs. This approach may be refined. For example, it does not make sense to add ELIAs of two well investigated substances where one substance shows exclusively local irritation at mucous membranes and the other substance shows exclusively effects to the liver. To derive ELIAs specific for the different target organs is a cumbersome task but is likely of higher toxicological relevance. That is,

$$\mathbf{\Sigma(C_i/ELIA_{i,j}) \leq 1},$$

where $ELIA_{i,j}$ is the ELIA of compound i against target organ j. At least local effects could be split from systemic effects, so the requirements would be

$$\mathbf{\Sigma(C_i/ELIA_{i,\,local}) \leq 1}, \qquad (2)$$

and

$$\mathbf{\Sigma(C_i/ELIA_{i,\,systemic}) \leq 1}. \qquad (3)$$

PROBLEM OF LACKING DATA

Several VOCs have only a limited toxicological database. This problem was also addressed in the concept of *Lowest Concentration of Interest* (LCI) for VOC-emissions from construction products (AgBB 2002). VOCs with limited data are compared to other compounds with the same functional groups. For example, if an aliphatic aldehyde is detected and no toxicological data are available it is assumed that the LCI of this aldehyde is the same as the lowest known LCI of an aliphatic aldehyde. As a pragmatic approach, it is recommended to proceed with ELIAs accordingly.

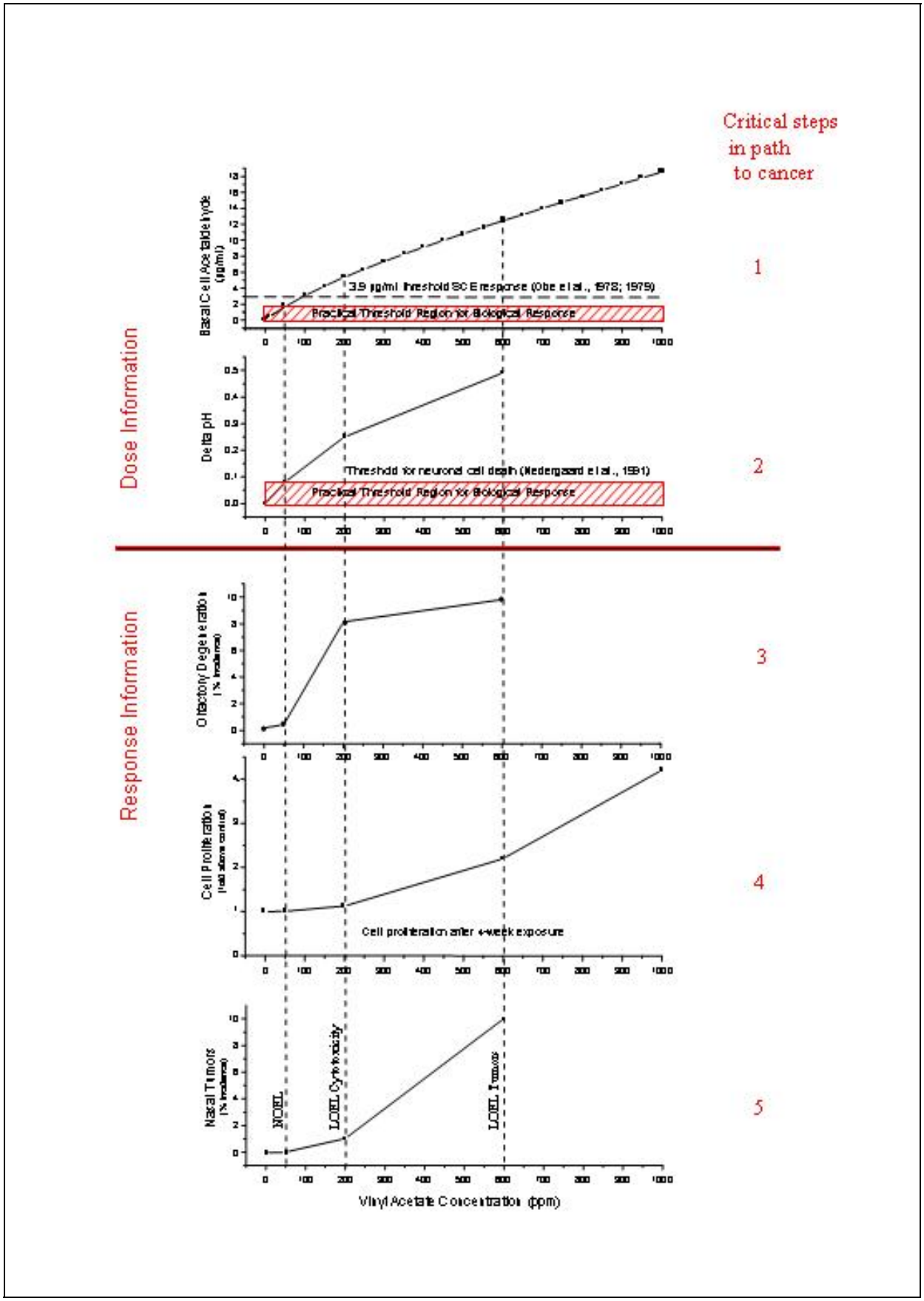

Fig. 4: Demonstration of a threshold mechanism for vinyl acetate in rats. *Panel 1:* Predicted steady state concentration of acetaldehyde at the basal cells, the progenitor cells of nasal cancer, in relation to *in vitro* doses that produce sister chromatide exchanges. *Panel 2:* Predicted pH_i changes in olfactory epithelium of the rat in relation to changes in pH_i that are

cytotoxic to neuronal cells *in vitro.* pH_i reduction is proposed to be the critical step leading to cytotoxicity. *Panel 3:* Olfactory degeneration in rats as a cytotoxic endpoint. Basal cell proliferation and the incidence of nasal tumors in rats is presented in *panels 4 and 5.* Olfactory degeneration (cytotoxicity) is observed at 200 ppm. Because acetaldehyde levels are only slightly above thresholds, there is no significant tumor response. At 600 ppm all thresholds are exceeded, cell proliferation is significantly enhanced and a significant incidence of nasal tumors is observed (from: Hengstler et al., 2003a).

REFERENCES

ACGIH, American Conference of Governmental Industrial Hygienists, Document of the Threshold Limit Values and Biological Exposure Indices, Volumes I, II, III, 1991

AgBB, Ausschuss zur gesundheitlichen Bewertung von Bauprodukten Evaluation Scheme: Health-related Evaluation for Volatile Organic Compound Emissions (VOC and SVOC) from Building Products, URL: http://www.umweltbundesamt.de/uba-info-daten-e/daten-e/voc.htm, 2002

Arand M, Herrero Plana ME, Hengstler JG, Lohmann M, Cronin A, Oesch F. Detoxification strategy of epoxide hydrolase the basis for a threshold in chemical carcinogenesis. *EXCLI J* 2003;22:22-30

Bauhof H. Messung organischer Emissionen im Kfz-Innenraum im Standverfahren. *VDI Ber*. 1994;1122:201-247

Crump K S. A new Method for Determining Allowable Daily Intakes. *Fund Appl Tox* 1984;25:854–871

Diehl JF. Von Delany zu de minimis – die Illusion des Nullrisikos. *Lebensmittel-Rundschau* 2003;99:359-360

ECETOC, Derivation of Assessment Factors for Human Health Risk Assessment. ECETOC, 2003; Technical Report No. 86, ISSN-0773-6347-86, European Centre for Ecotoxicology and Toxicology of Chemicals, Brussels

Hengstler JG, Arand M, Herrero ME, Oesch F. Polymorphisms of N-Acetyltransferases, Glutathione S-transferases, Microsomal Epoxide Hydrolase and Sulfotransferases: Influence on Cancer Susceptibility. in: Genes and Environment, ed.: Schwab M, Springer, New York, *Recent Results Cancer Res* 1998;154:47-85

Hengstler JG, Heimerdinger CK, Schiffer IB, Gebhard S, Sagemüller J, Tanner B, Bolt HM, Oesch F. Dietary topoisomerase II-poisons: contribution of soy products to infant leukemia? *EXCLI J* 2002;1:8-14

Hengstler JG, Bogdanffy MS, Bolt HM, Oesch F. Challenging Dogma: Thresholds for Genotoxic Carcinogens? The case of Vinyl Acetate. *Annu Rev Pharmacol Toxicol* 2003a;43:485-520

Hengstler JG, Bolm-Audorff U, Faldum A, Janssen K, Reifenrath M, Gotte W, Jung D, Mayer-Popken O, Fuchs J, Gebhard S, Bienfait HG, Schlink K, Dietrich C, Faust D, Epe B, Oesch F. Occupational exposure to heavy metals: DNA damage induction and DNA repair inhibition prove co-exposures to cadmium, cobalt and lead as more dangerous than hitherto expected. *Carcinogenesis* 2003b;24:63-73

Innenraumlufthygienekommission des Umweltbundesamtes (1996) Richtwerte fuer die Innenraumluft: *Basisschema. Bundesgesundhbl* 1996;11:422–426

Jung D, Bolm-Audorff U, Faldum A, Hengstler JG, Attia DI, Janssen K, Reifenrath M, Bienfait HG, Mayer-Popken O, Konietzko J. Immunotoxicity of co-exposures to heavy metals: In vitro studies and results from occupational exposure to cadmium, cobalt and lead. *EXCLI J* 2003;2:31-44

Kalberlah F, Hassauer M. Vergleich der Verfahren zur Ableitung gesundheitsbezogener Wirkungsschwellen (Benchmark – NOAEL). Abschlussbericht Forschungs- und Entwicklungsvorhaben FKZ 201 65 201/01, Umweltbundesamt, Bismarkplatz 1, D-14191 Berlin, Freiburg/Berlin, November 2003.

Oesch F, Hengstler JG, Fuchs J. Cigarette smoking protects mononuclear blood cells of carcinogen exposed workers from additional work-exposure induced DNA single strand breaks. *Mutat. Res* 1994;321:175-185

Streffer C, Bolt H, Follesdahl D, Hall P, Hengstler JG, Jakob P, Oughton D, Prieß K, Rehbinder E, Swaton E, Low dose exposures in the environment. Springer-Verlag, editor: C. Streffer, p. 83-180, Heidelberg, 2004

Technische Regeln fuer Gefahrstoffe 901 (2001) Begründungen und Erläuterungen zu Grenzwerten in der Luft am Arbeitsplatz. Bundesanstalt fuer Arbeitsschutz und Arbeitsmedizin, Postfach 170202, 44061 Dortmund, Germany

Technische Regeln fuer Gefahrstoffe 403 (1989) Bewertung von Stoffgemischen in der Luft am Arbeitsplatz. Bundesanstalt fuer Arbeitsschutz und Arbeitsmedizin, Postfach 170202, 44061 Dortmund, Germany

von Mach MA. Primary biliary cirrhosis in classmates: Coincidence or enigmatic environmental influence? *EXCLI J* 2002;1:1-6

Wiesmueller G. A Sick Building Syndrom. *ErgoMed* 1997;21: 69–88