Investigation of Health Hazards of Chemical Compounds in the Work Area (S0108 / M019)

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The former Division Interaction of Carcinogens with Biological Macromolecules was headed by H.W. Thielmann until his retirement (1999). The activities granted by the Bundesamt für Strahlenschutz and for the DFG Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area were continued by him.

1. Does individual radiation sensitivity gauge individual radiation risk in occupationally exposed persons?

Part II: Development of an in-vitro test system for assessing radiation sensitivity

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A new measure of DNA repair in the single-cell gel electrophoresis assay (comet) assay

Since its introduction by Östling & Johanson 1984, and independent modifications by Singh et al. and Olive et al., the comet assay has been widely used in genetic toxicology, environmental biomonitoring, molecular and human epidemiology and clinical investigations. However, the comet assay is still not accepted as a standard assay (e.g. by OECD) since the problem of quantitating DNA damage/repair in single cells is has not been solved. Presently, conventional evaluations are done in a mere “yes” or “no” manner, and DNA migration is described in qualitative terms.

Therefore, this activity, which has been supported by the Bundesamt für Strahlenschutz (Project: StSch 4116), focussed on developing a new and comprehensive measure of DNA damage/repair, assessed by the comet assay, which is based on all information contained in the dose/time-response surface observable in the experiment. On the basis of their investigations, the scientists of the project propose to establish a limited set of dose- and time-response curves using lymphocytes of individual patients, and to exploit the slopes of the curves. The dose/time-response data form a surface, for which a twofold derivative with regard to both dose and time, can be derived. The resulting term, 2D, integrates all dose/time-response data into one comprehensive term [1,2]. For computation, which includes linear regression, an SAS/AJ-based program “Comet Assay” was developed. This program is freely accessible through the Internet.

The new method was applied to data obtained from 25 breast cancer patients to be assessed for their radiation sensitivity. The 2D measures were computed for the four known damage measures, i.e., tail moment, tail length, tail DNA and tail inertia. These measures were found to be highly correlated. It was further established that, e.g., the proportional hazard model can be applied to the comet dose-time-response data [1,2].

For research activity on gene expression in premalignant rat liver cells [3], see Prof. Dr. P. Bannasch (“Hepato- carcinogenesis”). Mutational alterations of DNA polymerase α [4] are described in: Priv.-Doz. Dr. O. Popanda “Gene variants in replicative DNA polymerases from tumor cells” (C0200/C010).

2. Activity for the Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area

H.W. Thielmann

Since 1996 H. W. Thielmann is a member of the Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (“MAK Commission”) of the Deutsche Forschungsgemeinschaft.

The most important practical results of the Commission’s work are scientific recommendations for the establishment of MAK values (“Maximale Arbeitsplatzkonzentration”) and BAT values (“Biologischer Arbeitsstoffs-Toleranz-Wert”), for the classification of carcinogenic substances and for the evaluation of embryotoxic and fetotoxic effects and of germ cell mutagens as well as the investigation and evaluation of analytical methods for controlling exposure and for examining observance of threshold values for health protection at the workplace. In addition, the Commission investigates further current problems of hazards to health caused by occupational exposures and proposes possible appropriate solutions.

The sole object of the Commission’s work is to protect, as far as possible and necessary, and in line with the most up-to-date scientific information, the health of workers and of their offspring. Only scientific arguments regarding health at the workplace are considered in discussions and decision-making. Other aspects such as competitive sociopolitical, economic, technological and other nonscientific reasons are excluded.

The results of the Commission’s work are published by the Deutsche Forschungsgemeinschaft. After publishing its work, the Commission contributes to fulfilling the constitutional obligation of the Deutsche Forschungsgemeinschaft to provide advice on scientific matters to parliaments and public authorities. The recommendations of the Commission are handed to the Bundesminister für Arbeit und Sozialordnung who examines them, also taking nonscien-
tific viewpoints into account, and who then makes them legally binding in an appropriate form, altered or unaltered, as a basis for health protection.

During 2001 and 2002 more than 300 chemical compounds were newly evaluated or reevaluated with the intention to establish MAK and BAT values and to categorize them with regard to carcinogenic or germ-cell mutagenic effects. Decisions were published in the List of MAK and BAT Values 2001 and 2002 [5, 6], and handed to the federal Ministerium für Arbeit und Sozialordnung. For each compound, detailed scientific documentations were elaborated. Together, this work included more than 1800 pages. The documents were published in the monograph "Gesundheitsschädliche Arzneimittel - Toxikologische arbeitsmedizinische Begründungen von MAK-Werten" [7]. It is the policy of the Deutsche Forschungsgemeinschaft to assign authors' names only collectively to both the List of MAK and BAT Values and the Scientific Documentations, in order to protect authors (particularly those working in the industry) from being attacked for having recommended unwanted threshold limits (MAK or BAT values).

H. W. Thielmann is also a member of the Subcommittees “Classification of Carcinogens” and “New Mechanisms of Carcinogenesis” of the MAK-Kommission which develop and apply guidelines for the evaluation and classification of occupational carcinogens. The Subcommittee “Classification ..” shaped the new Classification System for Carcinogens in the Work Area. The new system has been adopted by the Deutsche Forschungsgemeinschaft and has been published in original and revised forms [see 5, 6].

Selected examples of chemicals that were categorized in 2001 and 2002 as carcinogens may be given here [5-10].

Category 1 (substances that cause cancer in man): arsenic and inorganic arsenic compounds, nickel and nickel compounds (as inhalable dust/aerosols).

Category 2 (substances that are considered to be carcinogenic for man): cobalt and cobalt compounds (as inhalable dusts/aerosols), bitumen (vapour and aerosol), 1,4-dichlorobenzene, naphthalene.

Categories 3A and 3B (substances that cause concern that they could be carcinogenic for man but cannot be assessed conclusively): ethylbenzene, 4-methoxyaniline, biphenyl, vinyl acetate, glutaraldehyde.

Category 4 (substances with carcinogenic potential for which genotoxicity plays no or at most a minor part): di(2-ethylhexyl) phthalate (the MAK value was fixed at 10 mg/m³).

Category 5 (substances with carcinogenic or genotoxic effect, the potency of which is considered to be so low that, provided the MAK and BAT values are observed, no significant contribution to human cancer risk is to be expected): none; under consideration: vinyl chloride.

Detailed procedures were elaborated and published on the significance, use and derivation of MAK values [5, 6]. In particular, guidelines were given for the evaluation of carcinogenicity, sensitizing effects, systemic toxicity, risks during pregnancy, and germ cell mutagenicity. Descriptions of the procedures used by the Commission in the evaluation of these end points can be found in the appropriate sections of the series “Toxikologisch-arbeitsmedizinische Begründungen von MAK-Werten” [7] and “Occupational Toxicants” [8, 9].

It goes without saying that the work of the Commission has to be considered as a whole. Thus, the contribution of an individual member cannot be assessed separately.

Publications (* = external co-author)


