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CURRENT PRINCIPLES OF HYGIENIC STANDARDS SETTING. Part I

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Abstract: A critical analysis of the present situation with respect to hygienic standard setting is presented. The authors introduce requirements for developing scientifically based exposure limits for chemicals as well as differences between documentation of recommended exposure limits for the agents occurring in the working environment and in the communal environmental medicine.

Despite the efforts undertaken at the national and international levels in order to adopt similar values of recommended or enacted hygienic standards, considerable differences in this respect can still be observed. The values of determined hygienic standards vary not only between countries but also between agencies within the same country. This refers particularly to occupational exposure.

The rapid development of economic activities in the 20th c. and the accompanying increase in the number of occupational and non-occupational hazards have brought about the rejection of a theoretical principle stating that all agents potentially harmful to human health should be totally eliminated from the environment. This principles had been substituted with the concept of A.L.A.R.A. – as low as reasonably achievable – applied to exposure monitoring and risk management. The concept has become of particular significance in cases where exposure to agents of non-threshold and latent activity is involved.

A discussion is going on among the scientists over the procedure for setting exposure limits according to quantitative and qualitative indices and the interpretation of results of human and animal studies. Another matter under discussion is the application of uncertainty and safety factors in the final part of the procedure. The question is still open as to whether the recommended limit should refer to a certain value or a range of values, which is associated mainly with an arbitrarily assessed degree of uncertainty regarding the quality and completeness of data. It should be emphasized that even if complete and relevant to a given procedure data are

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available, there is always an element of doubt due to the fact that some decisions in standard setting are made in terms of a compromise. The compromise is related mainly to inadequate knowledge, this applies particularly to the evaluation of health effects of exposure; interpretation of epidemiological data; extrapolation of results from aimal studies; relevance of measuring techniques used for the determination of exposure, especially for varying-concentration exposure; lack of data on health effects of combined exposure; uncertainty with respect to regulation of chemical carcinogens regardless of their genotoxic, non-genetic and epigenetic activities even when high safety factors are used. The most systematic approach to all those deficiencies is presented in the paper by Z. Henschler (6). The application of uncertainty factors in relation to inadequate knowledge on the mechanism of chemical activity, incompletness of data from mechanism of chemical activity, incompletness of data from databases and their reliability as well as the arbitrary adoption of safety factors for the non-threshold agents, mostly carcinogens and mutagens, make standard setting a particular procedure. Therefore, it seems necessary to view the already adopted or recommended values of hygienic standards with special caution. The most rational approach to the problem of setting hygienic standards is represented by the American Conference of Governmental Industrial Hygienists (ACGIH, which advocates considering the values as guidelines rather than definite borders between the safe and unsafe. These guidelines may be subject to change even within a short period of time, depending on new evidence.

The lack of data on recommended exposure limits in some criteria documents (e.g. IPCS Environmental Health Criteria or Criteria Documents from the Nordic Expert Group) may be the proof that no common and definite approach to value derivation has as yet been developed (2,7). It seems to be desirable to discuss and adopt at least a basic procedure of deriving exposure limits both with respect to the working environment and communal setting media. The procedure should cover the following elements:

– complementing the descriptive part of study results with quantitative indices of the dose-effect or esposure-effect as well as dose-response and exposure-response relationships,

– determining the use of toxicokinetic and toxicodynamic data in the derivation of recommended hygienic standards,

– setting the methods for extrapolation of animal study results, including determination of human equivalent of the dose or exposure,

– calculating the safety and uncertainty factors.

It can be assumed that the procedure should be divided into several stages implemented according to the available data from data base. As the scope of the information for deriving hygienic standards increases the missing stages of the procedure could be incorporated. This would allow prompt and effective amendment of the recommended exposure limit. The method could also facilitate decision-making while the standards are put into practice on the basis of relevant legislation.

Requirements for developing scientifically-based limits of exposure to chemicals

The prerequisites for the derivation and verification of recommendations for exposure limits are usually known by the group of experts involved in the procedure. It does not mean, however, that they are observed. An essential condition is the

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collection and processing of data which can be a starting point for the derivation of proposals of standard values. The data should be compiled into a comprehensive documentation which should be reviewed and published. There are increasing requirements with regard to the scope and way of developing such documentation. The publication of the Commission of European Communities (CEC) specifies the requirements both with regard to preparing documentation on occupational exposure, data selection and contents of the document (1). The CEC recommends also the ways of references arrangement, including the list of publications quoted in the documentation and not quoted (with the reason for not doing so) as well as the basic data evaluated and the criteria applied.

The clear and systematic CEC presentation of requiremnts for developing occupational exposure limits (OEL) may be used as guidelines for respective activity; however, an extension of their contents should also be considered. One of the additional items could be a detailed procedure of deriving the recommended exposure limits, epecially in those cases where the underlying data come from human and animal studies. This aspect seems to be particularly significant in view of the fact that even the OELs in force are not adequately (less than 60%) underpinned with data on long-term occupational exposure (8). The other issue that the OEL documentation could be extended with, concerns data useful for carrying out preventive activities e.g. the kind and scope of medical examinations, individual protective measures etc. It can be assumed that the requirements for developing criteria documents can be determined on the basis of a comparison of CEC recommendations with the patterns presented in the Environmental Health Criteria or the Recommended Health-Based Occupational Exposure Limits published by WHO, and with the NIOSH and Scandinavian documentation (2–4, 6).

In view of the professional concern of the authors as well as the necessity of limiting the scope of the problem-area tackled in this paper we will confine ourselves to discussing requirements for setting occupational exposure limits for chemicals. It should also be mentioned that both the scope of the information necessary for deriving hygienic standards as well as its scheme in the documentation may depend on the concept and form assumed and the availability of data on the biological effects of toxic chemicals.

Although the requirements concerning the form of documentation, quoting literature and making references are undoubtedly important, the most essential seem to be the information referring directly to the chemical substance, occupational exposure and methods for its assessment, effects of exposure on humans and animals and quantitative data on toxicokinetics and toxicodynamics. The final part of the documentaton should include an analysis of such problems as: the gaps in knowledge, increased individual susceptibility in some groups of people, other existing standards as well as review data on the substance toxicity and dose-response relationship (risk characterization), and justification for the postulated value of exposure limit.

The documentation published by different agencies within the same country (e.g. NIOSH and ACGIH in the U.S.), different countries or groups of countries (Scandinavian countries vs. Sweden) vary with respect to the scope and structure of the information (2–5, 7). The most comprehensive information and a specific structure is characteristic of the NIOSH documentation, the example being the exposure limit recommendations for ethylene glycol monobutyl ether and ethylene glycol monobutyl ether acetate published in 1990 and as an abridged version in 1991 (3, 4).

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Taking into account the contents of the documentation, one may presume that the agency intends to provide the data to all possible seekers, not only the professionals. As part of this documentation referring to employers, employees and their representatives is usually omitted in other publications of this kind, it seems desirable to enlist the chapter titles and briefly comment on their contents.

1. Recommendation for standard – TWA value is given and, possibly, data on dermal exposure and sample analysis.

2. Exposure monitoring – recommendations for sampling and biological monitoring (if feasible) are defined.

3. Medical monitoring – contains recommendations for the employer to inform the occupational physician about the exposure, prepare a monitoring programme, make an inventory of protective measures and provide medical examinations by a licenced physician for the exposed workers. The duties on the part of the exposed worker are also specified. Separate sub-chapters discuss the kind and scope of pre-placement and periodical medical examinations.

4. Labelling and posting – defines the employer's duties with respect to informing the worker about occupational hazards, protective equipment, transportation and storage of harmful chemical in specially labelled containers, labelling of buildings, passages and workplaces, and use of individual protective measures.

5. Protective clothing and equipment – specifies the types of individual protective measures (eye and face protection, skin protection, respiratory protecion) requirements regarding the quality, control and maintenance of protective equipment; effectiveness of their use.

6. Informing workers about the hazard – specifies the employer's duties pertaining to hazard communication, organization of training for workers and supplying them with written information on hazard including data on toxic activity of the hazardous agent, its physio-chemical properties and protective measures to be used.

7. Engineering controls – defines the duty of carrying out technical control in order to maintain the concentration of the chemical below the recommended exposure level; specifies requirements for engineering measures to reduce the air concentration of the toxic agent. The chapter discusses general work practices that are to ensure the safety of workers, including their access to confined or closed spaces; development of emergency plans and procedures; principles of chemical storage and waste disposal.

8. Sanitation and hygiene – the chapter includes possible contraindications for food processing, storage, distribution and consumption; use of cosmetic and tobacco storage and use. The requirements for sanitary facilities, laundry and sanitation appliances are specified.

9. Recordkeeping – obliges the employer to keep records of exposure monitoring and medical surveillance. Exposure monitoring records should be maintained for 30 years and duration of employment; medical surveillance records should be kept for more than 30 years. It defines also the transfer and accessibility of records for the worker and authorised persons.

The issues touched upon in the first part of the NIOSH documentation are discussed again, though in a different context, in the final part entitled "Methods for worker protection" with relevant supplements. The final part contains the details of preventive procedures, technical criteria for ventilation facilities and protective

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equipment, methods for exposure monitoring and medical surveillance. Reference is made to the legal regulations issued by OSHA, NIOSH and some other agencies. The annexes present such data as: description of the methods for exposure control, instruction for manufactures concerning preparation of the material safety data sheet, methods of determination of the substance or its metabolites in the biological material and medical aspects of wearing respirators.

Undoubtedly both parts, i.e. the initial and final ones, of the NIOSH documentation are a valuable supplement to its fundamental part.

The fundamental part in the chapter "Assessment of Effects" clearly presents methodology of NOAEL selection and the way of deriving REL values from NOAEL for rats.

Fundamental part of documentation

The fundamental part of documentation dealing with determination of occupational exposure limits, developed in various countries and by various national and international agencies, reveals both the similarities and differences. The similarities are that irrespective of the chapters and sub-chapters arrangement they provide information on the substance identification and its physico-chemical properties, on the effects of exposure in humans and animals, toxicokinetic and toxicodynamic data (if available), as well as kinds of biological effects and analysis of the study results quoted. The main differences consist in that some documentations comprise neither the procedure of the recommended exposure level derivation nor the proposition of hygienic standard (WHO/IPCS – Environmental Health Criteria, Criteria Documents from the Nordic Expert Group, Scientific Basis for Swedish Occupational Standards, British Criteria Documents). There are also some other serious differences both in the assumptions adopted for the safety level and in. e.g.:

– documentation structure,

– amount of literature analysed and the degree of criticism in evaluation of the relevance of the literature data,

– methodology of deriving the recommended exposure limits and extrapolation of the data obtained in experiments on animals, uncertainty and safety factors determination,

– taking into account or disregarding some other factors in the final evaluation (such as sex, groups of particularly vulnerable persons).

– taking into acount all kinds of the biological action of the substance investigated,

– further procedure associated with changing the recommended exposure level into the administrative exposure limit.

All attempts to eliminate the existing difference in the documentations and particularly in their essential section seem to be very useful.

Therefore, guidance notes concerning the contents and layout of criteria documents published by CEC in 1992 should be adopted as a standard or an example to be followed when preparing the documentation mentioned for two reasons (1). Firstly, because these are the newest recommendations based on the modern approach to documents recommending exposure limits and, secondly, because the Commission has decided to limit the documentation to the review of the principal toxicological data and evaluation of their effect on workers' health – and

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CEC guidance notes refer just to the fundamental part of the documentation. Some other chapters, apart from that entitled "Content" deal with the way of preparation, information selection, and references.

According to the CEC guidelines, the fundamental part of the OEL documentation should consist of 12 chapters, including the bibliography. Although quoting the guidelines chapters titles and listing the issues they deal with, according to Appendix I inserted into the guidelines final part, will not substitute the original text, it may provide the reader some general but helpful hints how OEL documentation should be prepared to meet the up-to-date requirements. The content of this Appendix is as follows:

1. Substance identification
- name and IUPAC, RTECS, EINECS numbers
- name and CAS number
- EEC number and labelling
- synonyms and trade names
- chemical group, formula and structure (including all isomers), impurities
- molecular or atomic mass
- the range of composition variability for materials of variable composition

2. Chemical and physical properties
- aggregation state, form and colour
- melting point and boiling point (°C)
- specific gravity (at 20° C)
- vapour pressure/vapour density, saturation
- concentration in air
- solubility (water – fats)
- conversion factor (1 mg/m^3 = ... ppm; 1 ppm =... mg/m^3)
- odour and odour threshold
- acetanol – water partition coefficient (if applicable)
- particle/fibre size and size distribution
- flash point, inflamable limits and oxidative properties

3. Occurrence
4. Production and use data
5. Quantitative information on exposure and uptake
6. Measuring techniques and analytical methods
7. Toxicology

a) Toxicokinetics

uptake and distribution
- animals
- man

metabolic biotransformation
- animals
- man

elimination (biological half-life), biological monitoring.

b) Toxicodynamics

effect on different organs and systems, specifying for each item:
- human and animal data
- acute, subacute, chronic toxicity

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- route of application, dose, and covering:
  CNS
  lungs and respiratory tract
  cardiovascular system
  liver/kidney
- other effects (amongst others: metabolism, muscular tissue, endocrine sytem, hematology)
- skin
- mutagenicity – carcinogenicity
- reproductive effects
- immunotoxicity.

8. Gaps in knowledge
9. Groups at extra risk
10. Existing occupational exposure limits
11. Summary evaluation and recommendation for (a) scientifically based occupational exposure limit(s)
    - substance identification
    - occurrence and use
    - health significance
    - recommendation
    - key bibliography
12. Bibliography

In various places of the CEC guidance notes, attention is paid to the following principles that must be observed during the documentation preparation:

– critical selection of literature and critical evaluation of the results found there both in respect to their quality (reliability) and relevance as well as usefulness for justifying of OEL value proposition, based on sufficient scientific results. This refers especially to the data on exposure, measuring strategy and analytical methods; data on exposure effects (with particular regard to epidemiological data), target organs and effects selection:

– strict quantitative presentation of information including, among others, exposure level (taking into account exposure duration), exposure intervals and accompanying circumstances; quantities absorbed by various routes; metabolic efficiency; retention and biological half-life, presentation of elimination rate in time function depending on exposure parameters;

– need for summing up and drawing conclusions from chapters devoted to toxicokinetics and toxicodynamics taking into account the data of crucial importance for OEL value determination.

It must be admitted that the guidelines are sufficiently precise and determine uniform requirements for criteria documents preparation. Its only important deficiency is a lack of an appendix or separate document determining the way of deriving the OEL value, simaltaneously taking into account the toxicokinetic and toxicodynamic data obtained both in humans and in various animal species, as well as of the procedure for determining uncertainty and safety factors determination.

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Problems associated with documentation of the recommended exposure limits

In the case of recommended environmental exposure limits (Env. REL) significant progress has been achieved chiefly due to the Environmental Protecction Agency (EPA) in the USA. However, the question remains to what degree the procedure of deriving Env. REL, recommended by the EPA, may be used for the recommended OEL value determination? The question of whether in the case of carcinogens, any exposure limits should be determined, is still being discussed. This problem has been omitted in the CEC guidelines. Specifying in the sub-chapter "Toxicodynamics" only the indicators determing the toxic effect potential in the form of NOAEL, and LOAEL suggests that the recommended occupational exposure limits refer exclusively to the chemicals of threshold effect. The problem of factors inducing reproductive and developmental disorders and the method for taking them into account in OEL value deriving is still open and requires discussion although it is frequently skipped over in many documents.

It can be easily ascertained, that the requirements regarding the documentation on the scientifically justified recommended exposure limits comprised in the CEC guidelines notes may be fully taken into account only in those cases in which the scope of investigations aimed at determining the toxicity of the specific chemical substances includes all aspects listed in the guidelines and when the documentation is published in an unabridged form. According to the analysis results quoted by Zielhuis and Wibowo (8) only 9% of OEL values from among 686 taken into consideraton appeared to be reasonably well supported.

Analysing the problem of requirements that should be met when preparing the OEL documentation according to the CEC guidelines, many conclusions may be drawn. Two of them seem to be of particular importance.

As the full range of information and data specified in the guidelines refer to a relatively small group of chemicals for which the recommended occupational exposure limits have been determined (not to mention the substances newly introduced into production and use or which are planned to be introduced) – postponing OEL determination till obtaining a possibly full range of data is rather controversial and in fact it is not to be recommended.

Although a lack of complete data is anticipated in all documentation nevertheless the question is: what is the minimum scope of information or investigation which allows to begin work on OEL determination?

Considering the problem of documentations of scientifically justified exposure limits (OEL, Env. EL) it should be stressed that their proper preparation is a responsible and labour consuming task, which requires a considerable experience and competence of numerous group of experts involved in implementing the task. Despite the fact that some small countries have noteworthy achievements in that field (e.g. Denmark), it seems that intensive activity in that field (apart from big countries of high economic potential as e.g. the U.S.A.) which satisfies the needs in this respect may be successfully implemented by international agencies of global coverage, such as WHO, or by a group of countries such as the EC or group of Scandinavian countries. This does not deny the need for conducting experimental and epidemiological studies in particular countries nor the need for having the specialists in this field. The need for ensuring the scientific bases for exposure limits is so great that it can be satisfied only with a great international effort. Experts of

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particular countries should be responsible for the appropriate adaptation of international recommendations to the existing conditions.

Differences between documentation of recommended exposure limits for agents occurring in the working environment and in the communal environmental media

The documentation of the recommended Env. EL is significantly more extensive as compared to the OEL documentation and, in addition, it differs in the way data are interpreted. However, in some ways both documentation methods are similar. It is obvious that the chapters devoted to substance identification, its physico-chemical properties as well as those describing toxicokinetics in humans and animals are identical. The chapter presenting the analytical methods also specifies methods for determinating chemicals in the environmental media and in food. Part of the documentation devoted to the occurrence and quantitaive information on human exposure additoinally provides information on the substance content in the environmental media and it also includes a very important chapter describing the environmental distribution and transformation including biodegradation and/or bioaccumulation. In the environmental health criteria, the chapter discussing toxicodynamic is more extensive as compared to the OEL documentaton. Apart from the data on the exposure effects on humans, laboratory mammals and *in vitro* test systems, it also usually comprises the data on the substances toxicity to microorganisms as well as aquatic and terrestrial organism. The final remarks in environmental health criteria include both the evaluation of health risk in humans as well as the evaluation of the adverse effects produced in the environment.

Approaches to deriving of the recommended exposure limits

Generally, all approaches adopted for deriving the recommended exposure levels (REL) are based on the assessment of the risk of occurrence of some changes in health status of humans either in the form of adverse effect or a prodromal symptom of such an effect.

The approach to evaluating the risk associated with systemic toxicity differs from the one used in evaluation of the risk induced by the factors of non-threshold action such as e.g. carcinogens.

The hypothesis of individual threshold has been put forward with regard to the factors exerting a sytemic effect. It sumes that some levels of exposure or doses absorbed (from 0 value to the determined value) may be tolerated by the organism without a significant probability of adverse effect or prodromal symptoms.

The very concept of adverse effect is not precise and it depends on the definition of health. Actually external factor, such as e.g. chemical substance after penetrating the organism, even in a small quantity, may produce many changes differing from the normal state. However, those changes may differ in the degree of their importance for human health or even be unpredictable if the toxic effect mechanism has not been studied. The recommended exposure limit is usually based on only one measurable toxic effect considered to be the most sensitive among some other changes and, at the same time., the one which affects the normal functioning of the organism. This effect has been determined to be critical, and a system or organ prone to developing such an effect is called a critical system or organ and the concentration (sometimes the one in critical organ or system) – the critical concentration.

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In the case of carcinogenic factors such as chemical carcinogens or ionizing radiation, in the early 60's it was assumed that they had no threshold action. It means that every exposure to such factor, even at a very low level (theoretically even one not exceeding one carcinogen particle) may be conducive to cancer development. Up till now, it has been a controversial problem, among others, due to the fact that single particles have very small chance to reach the receptor. In addition, it can be epidemiologically proved that low levels of exposure to carcinogens do not produce a noticeable effect, at least in the period of observation of the strictly determined group of persons exposed. It is known that in the case of formaldehyde, the carcinogenic process starts when necrosis of the cells of mucous membrane epithelium followed by their regeneration occurs, and this happens at high formaldehyde concentrations only. Nonethelless, the conception on the non-threshold effect of carcinogens has not lost its popularity and resulted in the fact that in many countries, the recommended occupational exposure limits for carcinogens are not determined. Instead it is recommended that when it is not possible to eliminate them, their concentrations be limited to the lowest possible level (ALARA). With regard to environmental media and food, the recommended exposure limits are based on the conception of the socially accepted risk, usually at the level from 10^{-5} to 10^{-8}. Hence, evaluation of the risk level is a basis for Env. EL for factors of non-threshold effect.

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