Health-based occupational exposure limits: An european experience in perspective

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Toxicity depends on the dose, and on the responding host as well. Workers health can be protected if there are well-founded exposure limits and compliance with them. This is the rationale for occupational exposure limits. However, totally safe exposure limits can be seldom obtained. Compliance, on the other hand, varies widely. A residual risk almost inevitably remains even because of the limited scientific knowledge and the considerable variation in the level of biological responses to a particular chemical substance, regardless of the airborne concentration. Ideally, OEL’s should fully satisfy the two demands of protecting health and avoiding unnecessary costs, which in practice is often not feasible. A compromise should be reached and this should be both science based and value based. The Scientific Committee on Occupational Exposure Limits (SCOEL) is an interdisciplinary advisory group of experts established in 1990 by the European Commission with the mission of identifying and proposing ‘health based’ exposure limits for occupational settings (OEL). Their experience is reviewed and discussed with special emphasis on limitations in data availability, challenges encountered and questions still open. The Committee devoted specific attention to carcinogenic and mutagenic substances for which two procedures have been followed. One is a risk assessment exercise that estimate, when data permit, the different risks entailed by different exposure levels, then living to regulators to decide which risk (if any) can be considered acceptable. The other approach exploits recent acquisitions on the different modes of action of carcinogenic agents, for some of which a threshold can be identified and a limit set. To be translated into policy, scientific evidence has to interplay with matters of values, costs, ethics and politics, but it remains a scientists’ responsibility to summarize and interpret in a valid and clear way all existing data and to explicitly state what is not known. The scientists, in addition, cannot be content with present knowledge but has to strive for further advancements and for bridging existing gaps. A particularly rewarding avenue of investigation would be the follow up in terms of exposure (external and internal) and health effects (health surveillance) of significant samples of exposed workers once a OEL has been established, adopted and the resulting regulation complied with. There is, in addition, the need to design and perform epidemiological studies particularly for characterizing risks for which evidence is limited. This holds especially for the numerous suspected carcinogens for which human data are missing or incomplete. All these objectives have in common a precondition, i.e., a tighter and more intense collaboration of different disciplines (hygiene, toxicology, epidemiology, occupational and environmental health, statistics) from both the industry and academy settings.

Key words: Occupational exposure limits, european experience, health-based

Introduction

The contribution of science to the regulatory decision-making process is becoming more and more relevant, thanks especially to its increasing capability of identifying hazards, assessing exposure types and levels, and characterizing risks. When valid and complete information exists, the regulatory process can be based on scientific evidence weighed against other relevant criteria (economical and technical considerations, for example); instead, when scientific evidence is missing or incomplete, other criteria, e.g., precautionary considerations, may drive the balance [Grandjean, 2004; Kriebel, 2009; Martuzzi, Tickner, 2004]. I’d like to address the issue of health-based occupational exposure limits (HB-OELs), with the aim to recognize and discuss the merits and limits of this approach and to identify some recent advancements that might improve their scientific bases and their effectiveness in protecting workers’ health.

The HB-OELs concept

Back in 1948, the American Conference of Governmental Industrial Hygienists (ACGIH) expressed in a sharp statement what they thought was a health-based occupational exposure limits: “People vary greatly in response to drugs and toxic substances. Therefore, it is a figment of the imagination to think that we can set down a precise limit below which there is complete safety and immediately above which there may be a high percentage of cases of poisoning among those exposed. With these facts in mind the Committee has set values below which it is fair to expect reasonable protection and above which it is reasonable to expect that we can occasional cases of poisoning” [Breysse , 1991].

Two things emerge quite distinctively: the relevance of inter-individual variability, and the limitation of the scientific knowledge on which the limits are based. Somehow, both points still hold today.

Regulatory decisions are based on and justified according to a set of criteria including scientific evidence, technical feasibility, people’s perceptions and societal sustainability that are subject to change in time and space. The present scenario has three main features:

• high and widespread public awareness of environmental risks and concern about their effects on human health and environment;
• new techniques capable of measuring exposure even at trace concentrations and of recognizing early functional, biochemical or genetic changes at the cellular and molecular level;
• change of the working population in terms of ethnicity, gender composition and age structure - and, hence, susceptibilities, education and values.

The concept of health-based limit might be illustrated by the continuum of events that brings from exposure to airborne toxicants to health impairment in the exposed subject [Foà, Alessio, 1998]. The external agent enters the body, undergoes...
metabolic transformation and reaches the target organ/tissue where it may initially cause biochemical and cellular changes with no health significance, or early transient and reversible effects.

If this chain of events is not interrupted at the earliest possible link, an overt health damage eventually occurs. The more completely we know the mechanistic steps linking environmental exposure to internal exposure and then to the appearance of early changes and non-adverse effects, the more feasible becomes the identification of the level of environmental exposure that complies with the definition of OEL. For this exact reason, the monitoring of airborne concentrations (ambient monitoring, AM) should always be supplemented by biological monitoring (BM) and health surveillance (HS) whenever they apply. A health-based limit has the inherent feature of being tentative and, hence, temporary. It must undergo revision as new relevant data appear and should undergo evaluation to confirm its appropriateness. Biological monitoring gives the opportunity to verify the effectiveness of the adopted environmental exposure limits against excessive intake. Health surveillance further verifies that the adopted protective measures do actually prevent even minor but potentially harmful changes in the exposed organism. Should they notwithstanding occur, health surveillance results set the need for further action.

In spite of that, too little attention has been paid to the longitudinal study of the long term relations of external exposure with internal exposure and early effects in exposed humans. The few existing observations are limited in time and size. There is, instead, a great deal of data being collected, however without valid and meaningful scientific design and goals. It is unfortunate, since we are missing a lot of valuable information in terms of scientific knowledge and policy effectiveness in this way.

The concept of "health based" should be viewed in relation with the expanding relevance of the evidence based approach in health interventions. As stated by Sackett, "Evidence based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients" [Sackett, 1996]. Evidence means "The available body of facts or information indicating whether a belief or proposition is true or valid" [Jawell, Abate, 2001] and it has henceforth been easily recognized that this same model was applicable not just to 'individual patients' but to exposed individuals and groups as well [Verbeek et al, 2002; Franco, 2005; Harris et al, 2008] and, more in general, to public health issues [Brownson et al, 2003]. However, it must be recognized that procuring 'evidence' is objectively more difficult in the field of prevention than in the field of diagnosis and therapy, but the exercise appears viable and should be performed [Vineis, 2000]. Yet, it is immediately understandable that to establish a health-based limit it is not sufficient to know the toxicokinetic and toxicodynamic properties of the agent of interest. It is further necessary to gather all pieces of relevant, valid information on experimental, epidemiological, environmental and clinical work to explore and document the relation that links exposure (type and dose) to the relevant effects (adverse, non adverse); to use appropriate models and methods to combine and evaluate the data which sometimes requires putting together observations and studies independently conducted and producing a combined quantitative evaluation; and then to verify the performance and the effectiveness of the selected value [Bertazzi, 2006].

One last feature of the health based occupational exposure limits that deserves specific mention rests with the fact that applying scientific data to policy decisions calls for a balanced distribution of the burden of proofs between type I error (when it has been concluded that an effect exists when in fact it does not exist: 'false positive' conclusion) and type II error (when it has been missed an effect that in fact exists: 'false negative' conclusion) [Hansson, 1998]. The burden of proof for regulatory applications differs significantly from the burden of proof that prevails for purely scientific purposes. In this latter case, type 1 error is considered the most serious error; failing to proceed could be reasonably deemed less harmful that moving in the wrong direction. In a regulatory context, instead, one is much more concerned of failing to protect against suspected health hazards even if the evidence is much weaker than that required by 'pure' scientific standards [Hansson, 1998; Rudner, 1953]. This is one of the arguments in favour of a precautionary approach, and this also explains why science cannot complete alone the complex and difficult task of establishing health-based occupational exposure limits.

A short account of the EU experience in establishing health based OEL's

The Scientific Committee on Occupational Exposure Limits (SCOEL) is an interdisciplinary advisory group of experts established in 1990 by the European Commission with the mission of identifying and proposing 'health based' exposure limits for occupational settings (OEL). I shall use this European experience, in which I have been participating since 1991, to illustrate the different steps of the HB-OEL definition process.

The objective in establishing health based OELs is "to set limits for exposure via the airborne route such that exposure, even when repeated on a regular basis throughout a working life, will not lead to adverse effects on the health of exposed persons and/or their progeny at any time (as far as can be predicted from the contemporary state of knowledge)" [Scientific Committee on Occupational Exposure Limits, 2009]. Health based OELs can be established in those cases where a...
review of the total available scientific data leads to the conclusion that it is possible to identify a clear threshold dose below which exposure to the substance in question is not expected to produce adverse effects. In their attempt to establish ‘health based’ limits for occupational exposures, SCOEL uses the following general procedure:

1. assemble all available data (background, human, animal, and experimental) on the hazards of the substance,
2. identify the adverse effects that may arise from exposure to the substance and among them those that should be considered crucial in deriving the OEL,
3. document the dose/response data for those effects in order to identify the ‘no observed adverse effect level’ (NO(A)EL) wherever possible, or otherwise the ‘lowest observed adverse effect levels’ (LO(A)EL),
4. identify whether a threshold toxicological model applies or whether the substance acts via a non-threshold mechanism,
5. establish a numerical value for an 8 h TWA OEL at or below the NO(A)EL (or, if this is not possible, below the LO(A)EL) incorporating an appropriate Uncertainty Factor (UF),
6. establish a numerical value for a STEL (if required),
7. establish a numerical value for a BLV (if required) 
8. document the entire process such that the rationale for the OEL is clear.
9. assess the technical measurement feasibility of the air and biological values recommended

In general, good quality human data are to be preferred to animal data, but may frequently either not be available or be inadequate scientifically. Human data falls into one of four broad categories: 1) individual case reports; 2) studies in human volunteers; 3) cross-sectional studies; 4) cohort and case-control studies. With the exception of 2), human studies generally suffer from poor characterisation of exposure and clear dose-response relationships are rarely demonstrated. In such instances it will be necessary to consider establishing an OEL on the basis of data derived from experiments in animals. Animal studies clearly suffer from the disadvantage that the species under investigation is not the human. Nevertheless, animal studies possess some clear advantages, particularly in respect of good characterisation of exposure, adequate use of controls, extensive pathological investigations and the potential to give clear indications of dose/response. The SCOEL considers that well conducted animal studies provide an acceptable basis for the establishment of ‘health based’ OELs, where human data are either not available or are inadequate.

In the process of extrapolating from a restricted human or animal data base to wider human populations, an ‘uncertainty factor’ (UF) is used. The UF is a number by which a defined NO(A)EL or LO(A)EL is divided to derive an approximate OEL, and reflects the overall uncertainty of the data base from which the health based OEL is derived. It comprises all adjustment aspects which are related to health (e.g. route to route, inter- and intra-species extrapolation). When developing limit values (e.g. average daily intake, or ADI, for food additives and contaminants, water/air quality standards) for lifetime exposure of the general public it is international-ly accepted that safety (uncertainty) factors of 10, 100 or 1000 should be used, depending on the available experimental and epidemiological evidence. (100 is usually used as a default value.) There is no generally agreed approach to the application of UFs in the process of establishing scientifically based occupational exposure limits. However, the following factors are relevant:

- the working population is less heterogeneous than the general population. In particular very young, sick and old people are not part of an occupationally exposed population,
- the working population is commonly exposed to airborne chemical substances for approximately 8 hours per day, 5 days per week, 240 days per year for a working lifetime (up to 45 years). This contrasts with daily uptake for a full lifetime, for which ADI and similar limits are developed.
- in EU countries the health of workers should be controlled by periodic health surveillance and monitoring programmes.

For the above reasons, for the development of scientifically based OELs it is often appropriate to apply lower UFs than those used to develop limit values for the general population. When adverse health effects (immediate or delayed) are not adequately controlled by compliance with an 8 hour TWA, short term exposure limits (STEL) are needed. This is likely for substances for which a critical effect is observed following a brief exposure (e.g. nuisance, irritation, CNS depression, cardiac sensitisation). The STEL is a limit value above which exposure should not occur and usually relates to a 15 minute reference period. The STEL is not a ‘ceiling’ value (value that should not be exceeded at any time during the work period or shift).

Chemicals may enter the body through the skin or the gastrointestinal tract, in addition to the inhalation route. Inadequate personal hygiene or inappropriate protective clothing may in such circumstances lead to a body burden significantly higher than which would have occurred via the inhalation route alone. In addition, inter-individual variation in toxicokinetics, as well as in other physicochemical and biological factors, may lead to differences in the amount absorbed for a given atmospheric concentration. Also, there may be intra-individual variations in exposure, due to changes in the working conditions within a shift. Biological monitoring may be able to take all these factors into account, as well as covering any non-occupational exposure, but for the majority of the external agent data are too limited to support a biological monitoring method and a derived BLV. As a general rule, SCOEL sets biological limit values (BLV) for compounds with a skin notation as a priority. The rationale for SCOEL’s BLVs is quite similar to that of ACGIH for Biological Exposure Indices BEIs® which document an individual’s “uptake” of a chemical. “BEIs® represent the levels of determinants that are most likely to be observed in specimens collected from healthy workers who have been exposed to chemicals to the same extent as workers with inhalation exposure at the TLV®…..The BEIs® generally indicates a concentration below which nearly all workers should not experience adverse health effects”. [ACGIH, 2005].

Occupational exposure limits may be used for a number of purposes. The principal intended use is to provide standards or criteria against which measured exposure levels in existing workplaces may be compared in order to ensure that, as far as the current state of knowledge permits, control is adequate to protect health. They may also be used for design purposes, to ensure that new plants and processes are engineered in such a way that exposures can be controlled at levels which will not damage health. They should not be used as a basis for assessing the acceptability of non-occupational exposure or for simplistically comparing the ‘toxicity’ of one substance with that of another. Correct and appropriate use of OELs in practice demands considerable knowledge and experience, particularly in cases where there is exposure to more than one substance (contemporaneously or sequentially); where routes of exposure other than inhalation may be significant; and the working patterns (e.g. shift system/exposure duration) are non-standard.

Main limitations, challenges and open questions with this approach

In stating their objectives, SCOEL recognizes two main limitations. One is that “where it is apparent that a significant proportion of the potential exposed workforce might or will be more sensitive to a substance, because of their underlying physiological condition, then the recommendation of SCOEL will make allowance for this enhanced sensitivity.” (ACGIH already in 1948 recognized that “people vary greatly in response to drugs and toxic substances” and has since permanently stressed and expanded the concept).

The second limitation stems from the fact that commonly there are not indisputable empirical grounds on which to base a definite assessment that a given exposure is safe, and hence: “It should be emphasised that it is always prudent to reduce exposure as far below OELs as can reasonably be achieved, in order to provide the greatest degree of health protection.” [Scientific Committee Group on Occupational Exposure Limits, 2009].

How should and could we cope with this scientific uncertainty that may undermine ours and people’s confidence in the established limits?

When a threshold cannot be established

This is the step that most vividly reflects scientific uncertainty. The impossibility to ascertain a threshold may occur for any of the following reasons:

- a non-observed adverse effect level (NOAEL) or a lowest observed adverse effect level (LOAEL) cannot be identified simply because the available data are not sufficient or sufficiently valid
- the nature of the substance suggests that a no-effect level does not in fact exist but that any level of exposure may carry some finite risk
- there are people responding below the identified ‘average’ threshold. The established limit is, therefore, of no value to them.

The first case is, in practice, the simplest one. In the absence of sufficient and/or valid data the Committee recognize their inability to establish a health-based OEL. If, however, good data exist from animal experiments, the Committee will use them and apply a ‘high’ uncertainty factor in deriving a OEL.

The second case refers to substances possessing properties such as genotoxicity, carcinogenicity and respiratory sensitisation for which it is not applicable, on present knowledge, the notion of threshold of activity. In such instances it must be assumed that any level of exposure, however small, might carry some finite risk. Two approaches have been used by SCOEL, a risk assessment approach by which a series of exposure levels associated with estimated risks are calculated; and a mechanistic approach which takes into consideration different modes of action for substances having the same properties. I shall use carcinogens as a relevant example.

Risk assessment. With this approach, no attempt is made to identify health-based limits, under the assumption that for recognized carcinogens the dose-response relation is linear and no threshold exists. Instead, whenever existing data permit, a risk assessment procedure is implemented in order to estimate the different risks entailed by different degrees/levels of exposure. An example was 1,3-butadiene [Scientific Committee Group on Occupational Exposure Limits, 2003; Zocchetti et al, 2004]. Estimates of leukaemia risk in terms of SMR’s and excess deaths were based on published dose-response models [Delzell, 2001]. A risk coefficient (β) per unit of exposure was estimated with two different methods. One was based on excess relative risk “linear model” without a threshold: To obtain the risk coefficient per unit of exposure, each observed excess risk (RR or SMR-1) was divided by the associated cumulative exposure. The second method was a “step model” in which the risk coefficient per exposure unit remained constant in a certain range of exposure and then changed abruptly (step) moving to the next range. The number of expected deaths from leukaemia in the absence of the exposure of interest was estimated in a reference male population (England and Wales) with a life-table approach, taking into account the mortality decline that naturally occurs in an ageing population.

Assuming that exposure lasts for a 40-year working life (between the ages of 20 and 65), the number of predicted leukaemia deaths associated with different cumulative exposure to 1,3-butadiene were calculated, using the estimated coefficients indicating the excess relative risk for each ppm of cumulative exposure, for a population of 1,000 exposed male workers between the ages of 20 and 85. Predicted and expected deaths were compared, and results expressed as either additional deaths (predicted deaths - expected deaths) or excess SMR (predicted deaths/expected deaths). The “step model” was considered the most appropriate. Excess deaths and excess SMRs were associated with lifetime exposure to 0.1, 0.2, 0.5, 1.0, 2.0, 5.0, 10 ppm of BD. As an example, the table below summarises the “step model” estimates for exposure to 1.0 ppm under various exposure scenarios.

Table 1: Estimated lifelong excess leukaemia deaths every 1000 workers exposed for a working life to 1ppm of 1,3-butadiene (BD) under different exposure-response scenarios published by Delzell et al. 2001 (Zocchetti et al. 2004).

<table>
<thead>
<tr>
<th>Exposure Scenarios and relevant tables with Dose-Response data (Delzell et al. 2001). deaths for exposure to 1 ppm</th>
<th>Excess leukaemia BD=1,3-butadiene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table 2, single agent</td>
<td>1.02</td>
</tr>
<tr>
<td>Table 2, multiple agents</td>
<td>1.53</td>
</tr>
<tr>
<td>Table 2, single agent, BD total peaks &gt; 100 ppm</td>
<td>7.13</td>
</tr>
<tr>
<td>Table 2, multiple agents, BD total peaks &gt; 100 ppm</td>
<td>4.59</td>
</tr>
<tr>
<td>Table 6, single agent</td>
<td>0.77</td>
</tr>
<tr>
<td>Table 6, multiple agents</td>
<td>1.19</td>
</tr>
</tbody>
</table>

From this calculations, the additional leukaemia risk associated with exposure to 1.0 ppm 1,3-butadiene over 40 years, according to the “step model”, and using the exposure estimates and their associated RR [Delzell et al, 2001], may be illustrated as follows: “In a population of 1000 adult males experiencing a mortality rate similar to that of the male population of England and Wales, occupational exposure to 1 ppm of 1,3-butadiene for a working life (40 years between the ages of 25 and 65), will cause from 0.77 to 7.13 extra leukaemia deaths, in addition to the 5 leukaemia deaths expected to occur between the ages 20-85 years in the absence of exposure to 1,3-butsadiene.” [Zocchetti et al, 2004].

Which level of risk might be considered acceptable is not under the remit of SCOEL to determine. This corresponds to other instances inside the European Commission, and requires further consultation with the pertinent bodies. The results are then forwarded to regulators who eventually come to a decision by weighting the evidence of the estimated risks at different exposure levels against complementary criteria, including risk ‘acceptability’. Those limits should not finally be considered ‘health based’, rather ‘pragmatic’.

The mechanistic approach is, instead, based on the recognition that, although the assumption of a linear dose-response relationship without threshold has been plausibly supported for many carcinogenic agents, other carcinogens may behave differently. SCOEL is considering a proposal which takes into consideration the ascertained or presumed different mechanisms of carcinogenic action [Bolt et al, 2004]. An array of possible modes of action have been proposed [Streffer et al, 2004]. As shown in figure 2, four categories of chemical carcinogens can be characterized at present.

**Figure 2: Scheme of a possible categorization of chemical carcinogens (A-D) according to their different mode of action (Bolt et al. 2004).**

Group A include non-threshold genotoxic carcinogens for which the linear non-threshold (LNT) model appears appropriate for assessing low-dose risk. If agent elimination is not feasible, regulations may then be based on the principle 'as-low-as-reasonably-achievable' (ALARA), on technical feasibility and social considerations. Examples of this type are ionizing radiation, vinyl chloride, naphthalene and wood dust.

Group B encompasses genotoxic carcinogens for which the existence of a threshold can be speculated but not sufficiently supported, at present, by data [Kirsch-Volders et al, 2003; Hengstler et al, 2003]. In this case, precautionary considerations will mostly lead to applying the conservative approach of a linear dose-response extrapolation, and the LNT model is used as a default assumption, based on the scientific uncertainty. Relevant examples being considered by SCOEL include acrylonitrile, benzene, naphthalene and diethyl-nitrosamine (DEN).

Group C includes genotoxic carcinogens for which a ‘true’ threshold that allows establishing a NOAEL. Insertion of an uncertainty (safety) factor permits the derivation of health-based occupational exposure limits. Examples are tumour promoters and hormones [Setzer, Kimmel, 2003]. SCOEL is also discussing chemicals such as chloroform and carbon tetrachloride.

Risk may vary among different populations and across individuals exposed to the same hazard. Differences in physical activity, respiratory rate, and body mass index are known to influence absorption and excretion of chemicals. Similar interferences on absorption and metabolism of chemicals have been described for other factors like sex, fat intake, alcohol consumption, medications, and in the case of co-exposures to complex mixtures of substances [Viau, 2002]. Other sources of variation of special relevance are inter-individual differences in uptake, biotransformation, mechanism of action, susceptibility to damage and repair capacity that can result in different dose-response relationships for different groups of individuals. This is the third condition where an effective health based limit cannot, at present, be established.

Group D lists non-genotoxic and non-DNA-reactive carcinogens that are characterized by a conventional dose-response relation with a ‘true’ threshold that allows establishing a NOAEL. Insertion of an uncertainty (safety) factor permits the derivation of health-based occupational exposure limits. Examples are tumour promoters and hormones [Setzer, Kimmel, 2003]. SCOEL is also discussing chemicals such as chloroform and carbon tetrachloride.

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Genetic components of inter-individual variability are of specific interest today [ACGIH, 2005; Miller et al, 2001]. In risk characterization, special relevance is recognized to genetic polymorphisms, i.e., sequence variations (inherited and induced) in genes encoding xenobiotic metabolism enzymes or DNA repair enzymes, which may modify individual response to chemical hazards [Kelada et al, 2003]. Although the number of reports on the impact of genetic polymorphisms on environmental exposure (carcinogens, especially) is steadily growing [Wild et al, 2008] examples of strong effect modification are limited.

Many environmental and occupational chemicals, toxicants and carcinogens require metabolic activation to exert their action. Metabolic polymorphisms can modulate individual response not by producing qualitatively different response, but rather by inducing a shift in the dose-response curve: a shift to the right modifies susceptibility by increasing the response level to the exogenous exposure (thus conferring protection) whereas a shift to the left elicits the same response at a lower exposure level. Metabolic polymorphisms represent common, low-penetrance conditions of altered metabolic function which become relevant to the disease process only when interacting with the exogenous (or endogenous) chemicals. They are not risk factors per se.

If we were in the position to include susceptibility variables in the limit value definition process, we could, at least in principle, be more effective in preventing the occurrence of adverse effects by protecting even particularly susceptible individuals. Instead of adopting a default “uncertainty” or “safety” factor we could introduce an actual inter-individual variability factor.

Consider the example of exposure to lead (Pb), using lead in blood as exposure markers. Delta-aminolevulinic acid dehydrata-
se (ALA-D) is central in lead toxicity and 80% of lead in blood is bound to it. ALA-D genotypes show polymorphic distribution in the population (wild type 1-1 present in 81.7% of the population; mutant heterozygous 1-2 in 16.8%; mutant homozygous 2-2 in 1.5%) [Battistuzzi, 1981]. Lead per se increases the average value of diastolic blood pressure. Polymorphism increases the affinity of ALAD to Pb and may modify its kinetic and hence toxico-dynamics [Onalaja, Claudio, 2000]. Using a cut-off of 300 micrograms of lead per litre of blood, the odds ratio (OR) for high diastolic blood pressure (>90 mmHg) was 1.91 (95CI% = 1.20-3.04) but when exposed subjects were stratified according to ALA-D genotype, the OR among those with mutant allele (ALAD ½, 2/2) was much higher than among the carriers of wild genotype (ALAD 1/1) was (OR = 6.82 vs, OR = 1.68) [De Palma et al, 2005].

**Table 2:** Relative risk (odds ratio, OD) of increased diastolic blood pressure for high vs. low lead in blood concentration in a group of 371 workers stratified according to δ-aminolevulinic acid dehydratase (ALAD) genotype, wild type (ALAD1-1, No. 272) and mutant (ALAD1-2/2-2, No: 61) (De Palma et al. 2005).

<table>
<thead>
<tr>
<th>ALAD 1-1</th>
<th>ALAD 1-2/2-2</th>
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<tbody>
<tr>
<td>Diastolic Blood Pressure (mm Hg)</td>
<td>Lead in Blood (µg·L⁻¹)</td>
</tr>
<tr>
<td>&lt; 300</td>
<td>≤ 300</td>
</tr>
<tr>
<td>&gt; 90</td>
<td>37</td>
</tr>
<tr>
<td>&lt; 90</td>
<td>79</td>
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<tr>
<td>116</td>
<td>156</td>
</tr>
<tr>
<td>OR [95% C.I.] = 1.68 [0.97-2.90]</td>
<td>OR [95% C.I.] = 6.82 [1.68-27.67]</td>
</tr>
</tbody>
</table>

Susceptibility factors should not be considered as if they were determining, causal factors of the effect. They are, instead, capable of modulating the expression of the actual risk factor which is the environmental exposure. [Khoury et al, 1988; Ottman, 1996].

A decade ago or so, somebody foresaw the advent of a "future molecular based primary prevention" [Shpilberg et al, 1997]. The first step in this approach is the genotypic screening of people for susceptibility status, followed by the application of "intensive prevention intervention" (more expensive) to those susceptible and "less intensive prevention intervention" (less expensive) to the much larger, less susceptible population. As a matter of fact, the time of this "molecular based prevention" does not seem to have come yet. It appears more prudent and more appropriate to implement exposure control at the population/group level as the first, fundamental prevention and safety measure; it can then be complemented by further measures for those who turn out to be hyper-susceptible.

**When a risk should be accepted**

Toxicity depends on the dose and on the responding host. Therefore, human health can be protected in dangerous environment if there are well-founded exposure limits and compliance with them. This is the rationale for occupational exposure limits. However, as we have seen, totally safe exposure limits can be seldom (if at all) obtained. Compliance, on the other hand, appears to vary widely. Ideally, OEL’s should fully satisfy the two demands of protecting health and avoiding unnecessary costs. But in practice this is not feasible. A residual risk almost inevitabilly remains and this is, somehow, inherent in the same definition of OELs. A compromise should be reached and this should be both science based and value based.

Two very different activities are required for determining how safe things are: measuring/assessing risk which is an objective but probabilistic pursuit; and judging the acceptability of that risk which is a matter of personal and social value judgment. Science can assess only the probabilities and consequences of events, not their value to people. There must be a bipartition of the regulatory task. The scientific part should be performed by experts in the relevant fields. The policy part derive is legitimacy by other sources, namely those representing the stake-holders (including the general public) to whom they are ultimately accountable [Lowrance, 1976].

To be translated into policy, scientific evidence (and uncertainty as well) has to interplay with matters of values, costs, ethics and politics. Central in this process is risk perception. Risk perception is the subjective assessment of the probability of a specified type of harmful event happening and how concerned we are with the consequences. To perceive risk includes evaluations of the probability as well as the consequences of a negative outcome. Perception of risk goes beyond the individual, and it is a social and cultural construct reflecting values, symbols, history, and ideology. Society seems to accept risks to the extent that they are associated with benefits, and are voluntary ("Everyone willingly takes risks"). [Sjöberg et al, 2004].

Despite the fact that dictionaries often define safe as “free from risk” we probably should accept the definition given by Lowrance, that ‘a thing is safe if its risks are judged to be acceptable’ [Lowrance, 1976]. The concept of “acceptable risk” evolved partly from the realization that absolute safety is generally an unachievable goal, and that even very low exposures to certain toxic substances may confer some level of risk. The term describes the likelihood of an event whose probability of occurrence is small, whose consequences are so slight, or whose benefits (perceived or real) are so great, that individuals or groups in society are willing to take or be subjected to the risk that the event might occur [Krewsky, 2006].

In the experience I’m referring to, the definition of “acceptable risk” or “sustainable risk” is not with the Committee of experts. Instead, SCOEL recommendations of HB-OELs and the summarised basis for their derivation are issued and circulated for wider consultation with government officials, industry and workers representatives. By this procedure, lists of occupational exposure limits are generated, consulted on and agreed by Member States and then published in Commission Directives. [Commission Directive 2009/161/EU].

Apart from this particular European experience with SCOEL, a general way to cope with the issue of science not being able to determine “absolute safety” is the precautionary approach (see above, Group B carcinogens as an example). The precautionary principle was introduced in the context of environmental and occupational health and safety as Vorsorgeprinzip or ‘foresight principle’ in the German Clean Air Act of 1974, as elaborated in
the 1985 report on the Clean Air Act [Boehmer-Christiansen, 1994]. In 1998 a further formulation was proposed, known as the Wingspread Statement on the Precautionary Principle: “Where an activity raises threats of harm to the environment or human health, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically” [Science & Environmental Health Network, 1998]. It has since been a useful way to focus attention on the particular challenges of taking actions in the face of scientific uncertainty [Kriebel, Tickner, 2001]. It denotes a general rule of public policy action to be used in situations of potentially serious or irreversible threats to health or the environment, where there is a need to act to reduce potential hazards before there is strong proof of harm, taking into account the likely costs and benefits of action and inaction [European Environment Agency, 2001]. It is also called foresight principle which connotes more positive, anticipatory action. [Kriebel, Tickner, 2001]

A precautionary approach requires in the first place to establish the level of proof needed to justify action to reduce hazards (the ‘trigger’ for action). This is not just an entirely scientific issue, as the judgment of ‘how much evidence is enough’ has social dimensions, and will depend on political and cultural concerns and on the consequences on inaction or acting in error. But a precautionary approach includes other elements such as:

- research and monitoring for the early detection of hazards;
- a general reduction of environmental burdens;
- the promotion of ‘clean production’ and innovation;
- the proportionality principle, where the costs of actions to prevent hazards should not be disproportionate to the likely benefits;
- a cooperative approach between stakeholders to solving common problems via integrated policy measures that aim to improve the environment, competitiveness and employment;
- action to reduce risks before full ‘proof’ of harm is available if impacts could be serious or irreversible [European Environment Agency, 2001].

The contribution of new markers

Although tools exist to cope with environmental risks even when science is limited, little doubt exists that prevention may be fostered by gaining insight into mechanisms through which environmental exposures produce adverse effects in humans. However, mechanistic studies do not suggest per se effective strategies to reduce risk. Therefore, the research on mechanisms of action should not be seen as alternative to research on control technology and population intervention strategies. It may rather complement that research by: (i) identifying and characterizing portions of the population needing special protection; (ii) assist in assessing reasonably effective health based limits for agents that cannot be banned; (iii) testing the effectiveness of measures already in place; (iv) pinpointing gaps in knowledge that need to be addressed.

Incorporating genetic and molecular markers into occupational safety and health research may allow more accurate exposure assessment, improved understanding of intermediate endpoints, and enhanced risk prediction. Polynuclear aromatic hydrocarbons (PAHs) are a typical example. One can measure PAH’s in ambient air through environmental or personal monitoring; the amount of PAH’s that enter the body might be assessed through internal dose markers; but the ability of PAHs to reach DNA and bind to it depends on individual metabolic capabilities (which are in part genetically determined) and to the individual ability to repair DNA damage. Molecular markers are therefore needed, at least to:

1. obtain exposure estimates at the molecular site of action, the so called biologically effective dose (e.g., DNA adducts) [Phillips, 2008];
2. take into account the genetically determined inter-individual biological variability which might open the way to new prevention policies, even at a “personalized” level.

The genes we are interested in most are those involved in the metabolism and detoxification of xenobiotics (including DNA repair for carcinogens), as seen before for lead and ALAD. Their effects is dependent on the presence of toxic agents. Their action affect the potency of those agents but have no influence on toxicity by themselves. They increase the susceptibility of the host to those toxicants. Future achievements in the study of genetically determined inter-individual biological variability might open the way to new prevention policies, possibly at a "personalized" level.

A new group of markers related to epigenetic changes have recently become particularly interesting [Bollati, Baccarelli, 2010]. Epigenetics investigates changes that alter the pattern of gene expression that persist across at least one cell division but occur without changes in DNA sequence [Wolffe et al, 1999]. Epigenetic mechanisms include:

1. alterations of chromatin structure mediated by methylation of cytosine residues in CpG dinucleotides (referred to as CpG islands)
2. modification of histones by acetylation or methylation
3. changes in higher-order chromosome structure.

Through any of these mechanisms, exogenous factors can influence genome function. DNA methylation, in particular, is involved in regulating many cellular processes, including chromatin structure and remodeling, X-Chromosome inactivation, genomic imprinting, chromosome stability, and gene transcription [Reik, Dean, 2001; Grewal, Moazed, 2003]. Generally, gene promoter hypermethylation is associated with decreased expression of the gene [Orphanides, Reinberg, 2002].

Epigenetics is at the focus of modern medicine since it can help to explain the relationship between an individual’s genetic background, the environment, aging, and disease. It can do so because the epigenetic state varies among tissues and during a lifetime, whereas the DNA sequence remains essentially the same. As cells adapt to changing internal and external environment, epigenetic mechanisms can remember these changes in the normal programming and reprogramming of gene activity [Feinberg, 2008]. Several environmental factors have been linked to aberrant changes in epigenetic pathways both in experimental and epidemiological studies. In addition, epigenetic mechanisms may mediate specific mechanisms of toxicity and responses to certain chemicals. In-vitro studies have established an association between DNA methylation and environmental metals, including nickel, cadmium, lead, and particularly arsenic; for a review see [Wright, Baccarelli, 2007]. We investigated whether DNA methylation changes are induced by low-benzene exposure in peripheral blood DNA of gasoline station attendants and traffic police officers. Airborne benzene exposure was associated with a significant reduction in LINE-1 and Alu methylation (proxi of DNA total methylation), and was also associated with hypermethylation in...
p15 and hypomethylation of the MAGE-1 cancer-antigen gene [Bollati et al., 2007]. Recently the effects of exposure to particulate matter with aerodynamic diameters <10 μm (PM10) on Alu and LINE-1 repeated elements and gene-specific methylation in workers of a steel plant were investigated. Promoter methylation of the iNOS (inducible Nitric Oxide Synthase) gene was significantly lower in post-exposure blood samples compared to baseline, whereas long-term exposure to PM10 was negatively associated with methylation in both Alu and LINE-1 [Tarantini et al., 2009]. We also showed that exposure to black carbon (BC), a marker of particles from vehicular traffic, is associated with decreased DNA methylation in LINE-1, measured in 1,097 blood DNA samples from the Normative Aging Study (NAS), an investigation of elderly men in the Boston area [Baccarelli et al., 2009]. Such changes may reproduce epigenetic processes related to disease development and represent mechanisms by which xenobiotics affect human health [Baccarelli, 2009].

In spite of the current limitations, available evidence supports the concept that Epigenetics holds substantial potential for furthering our understanding of the molecular mechanisms of environmental toxicants, as well as for predicting health-related risks due to conditions of environmental exposure and individual susceptibility.

**Concluding remarks**

In occupational and environmental health & safety sciences, evidence may accumulate slowly and only reach a level of certainty sufficient for policy-making after decades of research. It is a decision makers’ duty to identify balanced ways to take action to reduce risk even before conclusive scientific evidence is available. It is a scientists’ responsibility to summarize and interpret in a valid and clear way all existing data and to explicitly state what is not known. The scientists, in addition, cannot be content with present knowledge but has to strive for further advancements and for bridging existing gaps.

The study of the relations of external exposure with internal exposure and early effects in occupational exposed humans is not high in the scientific agenda. Numerous reasons can be identified including: few research funding opportunities; feasibility being a real-life not laboratory-based research; the interest and availability of industry to cooperate; the lack of links and exchanges between occupational health & safety in-field operators and scientist (toxicologist, epidemiologist, hygienist); the urgency put on regulatory processes but not, at the same time, on knowledge improvement and research innovation.

A particularly rewarding avenue of investigation would be the follow up in terms of exposure (external and internal) and health effects (health surveillance) of significant samples of exposed workers once a OEL has been established, adopted and the resulting regulation complied with. The significance of the results would be twofold. They represent an evaluation of the effectiveness of the adopted intervention and might shed further light on the exposure-response relation even in the long run.

More in general, there is the need to design and perform epidemiological studies particularly for characterizing risks. This holds especially for the numerous suspected carcinogens for which human data are missing or incomplete, for example, lists 2A (no. 58 agents) and 2B (No. 248 agents) of the International Agency for Research on Cancer accessible at: http://monographs.iarc.fr/ENG/Classification/index.php. They include a number of agents which have been in use in the past in occupational settings, but for which satisfactory epide-

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