Reference Limits in Occupational Toxicology
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Two categories of reference limits can be discerned in biological monitoring: The first category identifies individuals who have been exposed to a toxic agent at work, and is based on the distribution of the concentration of the agent or its metabolite in the population that has not been exposed to the agent at work. The second category, for which the term biological action level (BAL) is proposed, provides a guideline on the level of exposure that is acceptable. These levels may be either directly health-based or derived from good working practices. Thus BAL is a biological equivalent for the generic term occupational exposure limit. BAL should be independent of legal overtones, and implies that workers’ exposure should be reduced.

Indexing Terms: biological action level/occupational exposure limits

Biological monitoring (biomonitoring) has been defined as “measurement and assessment of agents or their metabolites either in tissues, secretions, excreta, expired air, or any combination of these to evaluate exposure and health risk, compared to an appropriate reference” (1). Results from biomonitoring analyses are interpreted by comparing them with reference limits. Two categories of reference limits exist: The first resembles reference limits in clinical chemistry and identifies exposed people; the second sets limits for acceptable exposure to chemicals. The first category is based on an appropriately specified model of distribution (3) derived from analytical results (reference values) for a sufficiently large defined sample (reference sample) of a population (reference population). Except for the occupational exposure in question, the members of the reference population are similar (in terms of ethnicity, sex, age, environmental exposures to dietary factors, air pollution, smoking, and other social habits) to the occupationally exposed population. For most chemicals, however, the lower reference limit derived from unexposed individuals is not known: analytical methods rarely have a sufficiently low detection limit to quantitate very low concentrations of xenobiotic substances in biological materials such as those associated with adventitious exposures to potentially harmful chemicals. Therefore, in occupational toxicology the term reference interval is seldom used and may not even be understood by occupational hygienists and physicians. Instead, interest is focused on its upper bound, the upper reference limit (URL). For many toxic industrial chemicals, the URL is equal de facto to the limit of detection of the relevant analytical method.

In recent years, biomonitoring has also been used increasingly to explore the occupational exposure of groups of workers. It is apparent that, to characterize the exposure of groups rather than individuals, simple comparison to the URL with its given confidence limits is not appropriate. Instead, the distributions of the analytical results obtained in the allegedly exposed group should be compared with the distribution of the reference values by appropriate statistical techniques. As a prerequisite for this approach, laboratories that perform biomonitoring analyses should provide proper information on the distribution of the reference values in unexposed subjects, i.e., the number of data points and the form and parameters of the distribution.

It must be emphasized that because of different environmental settings, the actual values for URLs may vary from one geographical location to another. This has been documented extensively for lead and cadmium (4, 5). Moreover, changes may occur over time, as seen in the concentrations of lead in the blood of selected populations in several countries in recent years (6, 7); personal habits, notably smoking, are known to influence the concentrations of exogenous chemicals, such as cadmium and benzene, in body fluids (7, 8). Thus, in principle, URLs should be determined for each geographic area, with concomitant environmental, nonoccupational exposures being taken into account. Often reference values for URLs have been collected for ad hoc assessment of the occupational exposure of a group of workers; the number of such values is small, and sampling of the affected populations has been inadequate. Therefore, an analysis of distribution and the subsequent setting of the reference interval cannot be done adequately.

The second set of reference limits is based on a judgment of what is and what is not an acceptable exposure. Thus, they are equivalent to standards and guidelines given for concentrations of chemicals in the workplace air, i.e., occupational exposure limits (OEL), and are not based on observed concentrations in a population. For these limits, the term biological action level (BAL) is proposed. Therefore, BAL is a value—usually expressed in terms of concentration—that should not be exceeded in occupational exposure. There are three ways in which a BAL may be developed: (i) from clinical, epidemiological, and toxicological studies on the relation between a measured concentration of a chemical or metabolite in body fluids and the health outcome (directly health-based BALs); (ii) from the existing OELs by determining the relation between workroom air chemical concentration and the concentration in the biological specimen (OEL-derived BAL); and (iii) from other experience with good working practices.

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2 Nonstandard abbreviations: BAL, biological action level, as defined in this paper; OEL, occupational exposure limit; and URL, upper reference limit.

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Directly Health-Based BALs

Directly health-based BALs are ideally derived from long-term follow-up studies of workers exposed for 8 h a day, 5 days a week, over their working lifetimes, and are defined as limits guaranteeing absence of adverse effects on health. This is the way in which the German Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area defines its biological tolerance values (Biologische Arbeitsstoff-Toleranz-Werte) (9). Obviously, such values are not easy to obtain with confidence; best validated, such BALs are probably now available for lead, cadmium, mercury, and carbon monoxide in blood, and cadmium, fluoride, and mercury in urine. Directly health-based BALs usually relate to a specific toxic end-point and are limited by the information that is available; thus, they may change when further data accumulate. For example, the BALs for urinary and blood cadmium that have been used in most countries are based on reasonably well-defined measures of the nephrotoxicity of cadmium (10). The fact that cadmium is now considered to be a human carcinogen (11) may well lead to changes in the BALs that are applicable to cadmium.

OEL-Based BALs

BALs based on OELs are derived mathematically as the concentration of the relevant chemical/metabolite in the chosen biological material that will occur in an average worker after an 8 h, time-weighted-average exposure at the level of the prevailing OEL. This is how the American Conference of Governmental Industrial Hygienists defines the biological exposure indices (12); it is also how the German Senate Commission defines the biological exposure equivalents for carcinogens (Expositionsequivalente für krebsverursachende Arbeitsstoffe) (9). Protection of health provided by the BALs derived from OELs thus depends on several factors: the appropriateness of the OEL (which almost always reflects a compromise between health protection and cost factors); the reliability of the estimate of the relations between the OEL and the BAL; and the appropriateness of the sampling strategy. The BAL derived from the OEL for a chemical with a short half-time in the body is crucially dependent on the timing of sample collection. It also should not be forgotten that the BAL is the best estimate of a concentration in the biological specimen equivalent to the OEL (from an empirical regression line that describes the relation between concentrations in workplace air and in the biological specimen). Therefore, the actual exposure for approximately half of a group of workers is in excess of the OEL even when compliance with the BAL is notionally 100%. However, most workplace standards aim at the protection of "most workers" (9, 12). Hence, the BAL and OEL are not commensurate. Furthermore, the uncertainty of the estimate varies widely between different chemicals; e.g., after exposure to styrene, the uncertainty is small for mandelic acid or mandelic acid plus phenylglyoxylic acids in urine (for which a large number of studies with concordant results have been published) but is quite large for styrene itself in urine (for which few studies have been published) (13).

BALs Derived from Good Working Practice

The good working practice-derived BAL is the result of a purely pragmatic process of defining the chemical/metabolite concentrations in biological specimens from workers exposed to toxic chemicals, when good working practices are adhered to. Thus, BAL may be set at a value that 90% of the workplaces have actually achieved. For chemicals that are extensively absorbed through the skin, this is usually the only way of deriving a BAL, and one that has been used by the British Health and Safety Executive (14).

The legal status of BALs differs among countries and among international organizations. The European Commission BAL on lead in blood is legally binding (16), but many other BALs are interpreted more as guidelines, and are implemented accordingly.

References