Biological Monitoring according to Directive 98/ 24/EC: chemical risk in hospitals

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Definitions

The main objective in occupational hygiene is the prevention from the effects of the exposure to chemicals and pollutants in the workplaces.

The preventioon tools are the definition and maintenance of acceptable exposure levels, and periodical evaluations of the workplaces and of the workers conditions.

This is achieved by monitoring the substances used in the workplaces, from the moment they enter the workplace upto the target cells in the workers' bodies.

The environmental monitoring performs risk assessment measuring the external exposure levels, mainly in air but also on surfaces, in water, soil, food etc. comparing them to threshold limit values (TLV).

The biological monitoring can be:

1. The monitoring of exposure, that measures the internal exposure levels (dose indexes) and possibly compares them to reference values **called biological exposure indexes (BEI)**
2. The monitoring of effects, that identifies early simptoms or disorders, still reversible reducing the exposure levels (**effect indexes).**

Biological Dose Indicators are defined as the concentration values of a substance or of its metabolites measurable in specimens collected in healthy workers (urine, blood, exhaled air, hair, saliva, exhaled air).

The route of exposure is how a toxic substance can enter the worker's body: occupational exposures are generally cronic, and are due to inhalation or skin contact.

Accidents can cause acute exposure, wrong habits like eating or drinking on the workplace can lead to ingestion.

Why biological monitoring?

Because it can be:

1. **Cheaper than the environmental:**

Environmental Monitoring requires: 8 hours sampling time in several points of the workplace; personal sampling, that involves workers carrying pumps; hygienists must stay on the workplace during sampling; sampling materials are expensive.

Biological Monitoring only needs 1 or 2 blood or urine samples per worker, collected in cheap disposable containers and sampling can also be made outside the workplace.

2. **Complementary to the environmental**

Biological monitoring completes the environmental one for:

- a full assessment of the occupational exposure
- chemicals that can be absorbed also through the skin
- non volatile chemicals (skin exposure only)

3. Necessary

Biological monitoring is indispensable for:

- Assess previously occurred exposure (like accidents)
- Evaluate non professional exposure
- Verify the effectiveness of personal protective devices
- Verify working procedures
- Consider variability sources: variability is due to:

- individual factors, like genetic differences, age, sex, body size, health condition, pregnancy, personal hygiene;
- confounding factors, like alcohol consumption, smoking, environmental air pollutants, water and food contamination,sinergic effects due to simultaneous exposures;
- logistic factors, like working rate and workload, use and efficacy of personal protection devices, microclimatic parameters like temperature and humidity.

4. **Compulsory**

The directive 98/ 24/EC gives a definition of Biological Limit Value and states that the Biological Monitoring must be integral part of the Medical Surveillance, when a Limit Value has been adopted.

There are 2 EEC lists of Indicative Occupational Exposure Limit Values (IOELV).

There are adopted limits for 63 chemicals (39/2000/CE), and proposed for more 26 chemicals.

Member states shall fix national Exposure limit values and Biological limit values, in accordance with the EEC list.

The ACGIH list of Biological Exposure indexes (BEI) identifies 63 exposure indexes with adopted limit values for 38 chemicals or classes, 7 proposed indexes for 4 more chemicals, and BEI and their limits undergoing studies for 28 chemicals .

The Deutsche Forshungsgemeineschaft (German State Commission) had already stated 60 limit values (BAT) for 43 substances or classes, 12 EKA values (reference values for carcinogenic substances) and 9 are under evaluation.

This will increase the need for validated reference analitical methods for the biological monitoring and for National or EEC reference centers to define the quality criteria for these methods.

Planning Biological Monitoring

The lungs are a fast and efficient introduction route for gases, vapours, aerosols and solid particles between 0.2 e 5 microns.

The skin, with its wide surface, is the introduction route for lipophilic substances, both if disperse in the air and by direct contact.

All substances after being introduced in the human body undergo biochemical processes that tend to increase their solubility in the body fluids and facilitate elimination. This helps their excretion, reducing the half-life and therefore the potential toxic effect.

The half life is the time needed for a substance to reduce its plasmatic concentration to one half.

Some substances can accumulate inside the body, like pesticides in fat tissue and lead in the bones.

All substances are excreted in urine, gaseous ones also though the lungs in exhaled air.

What to do? Chose the biological index on the basis of the kind of information needed (dose, effect, short time or long time exposure).

Where? The specimen is the biological material in which the indicator has to be determined. Urine is to be preferred as a less invasive sample. Urinary BEIs are often expressed as BEI/creatinine ratio. Very diluted or very concentrated samples have to be discarded.

When? The sampling time is determined on the basis of the half-life. Indexes that are determined after short times reflect the most recent exposure. Indexes that accumulates give information on the whole previous exposure.

How? Sample must be collected in suitable containers, correctly identified, transported and stored in conditions that guarantee their stability. Analytical tecniques shall be higly sensitive to perform trace analysis. Sampling and analytical methods shall be validated to allow corret interpretation of results and comparison with limits values, that involves determination of the following parameters:

- **Sample stability.**
- **Analyte recovery** from the biological media.
- **Precision** of the method or repeatability
- **Accuracy,** expressed as total recovery of a known sample
- **Sensitivity,** expressed as lowest detection or quantitation limit.
- **Specificity,** expressed as background noise or result of a blank.
- Interlaboratory circuits have to be performed, in order to evaluate the **method ruggedness**.
- **Reference Standard Materials** must be identified.
- **Reference values** must be determined if the indicator is not absent from non occupationally exposed populations.

Anticancer Drugs

This is a wide class of compounds, who is able to inhibit cell growth. Due to their mechanism of action, these substances can be genotoxic, oncogenic, mutagenic and teratogenic agents.

For each therapy one or more drugs are used, and therefore the personnel involved in preparing and administering the therapies is potentially exposed to many different molecules each day, mainly through skin contact.

In order to assess the risk of exposure, a careful inspection of the premises must be carried out, to verify the respect of guidelines for manipulation of these drugs, and both environmental and biological monitoring must be performed.

As for each of these substances the pharmacokinetik has been studied, it's possible to determine the substance itself or its metabolites in the biological fluids of the hospital workers. The most frequently used molecules are chosen as contamination indicators, and the scientific literature can provide analytical methods for the biological monitoring of occupational exposure to Ciclophosphamide, Iphosphamide, Methotrexate, and Platinum compounds.

The non modified substace is determined in the end shift urine samples, and the reference standard material is generally the drug itself. The most suitable analitical tecniques are reported in the following table:

Drug/indicator	*Media*	*Analytical tecnique*
Ciclophosphamide Iphosphamide	End shift urine	HPLC/MS/MS
Metotrexate	End shift urine	HPLC/MS/MS
5-fluoro-uracil or α-fluoro-β-alanine	End shift urine	HPLC/MS/MS O GC/MS
Taxol	End shift urine or plasma	HPLC/MS/MS
Platinum Compounds	End shift urine or plasma	ICP/MS

Volatile anaesthetics

The personnel working in operating theaters is exposed to the risk of inhaling anaesthetic gases. Many toxicology studies indicate that these substances are toxic to liver and kidney, for the nervous system and the bone marrow.

In the table herebelow the biological monitoring information are reported:

Substance	*Media*	*Analytical tecnique*
N2O	End shift urine	**GC/MS**
Halogenated	End shift urine	**GC/MS**

Other Substances

Several other substances are used in hospitals, for different purposes, and they have to be considered in assessing the risk of exposure to chemical agents.

For some of them there are literature data and analytical methods available, but for more, studies have still to be promoted.

The table reported summarizes the most commonly used substances:

Substance	*Indicators*	*Media*
Ethylene oxide (sterilization)	Hemoglobin adducts Hematological changes	Blood (after 4 months of exposure)
Formaldehide (sterilization, laboratories)	Cytogenetic indexes (micronuclei)	Blood (previous exposure)
Glutaric aldehide (sterilization)	Not studied	----------
Mercury vapours (thermometers, sfingomanometers, dental cares)	Hg	Urine, blood, hair (total exposure after several months)

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