INTRODUCTION

According to an evaluation made by the International Agency for Research on Cancer (IARC), 66 agents or exposures have been recognised as human carcinogens. About 66% of all cancer cases occur in people over 65 years of age.

The implementation of effective measures for reducing the human disease burden depends primarily, although not entirely, on our knowledge of what causes the disease. For instance there is a general consensus that about 50% of cancers would be avoided if the existing aetiological knowledge was applied.

In most western countries the objectives of biological monitoring is to secure the health of the worker. Generally monitoring toxic chemicals in the air of the workplace is commonly used as a measure of the degree of exposure. However, the information obtained from air monitoring is insufficient if the chemical penetrates the skin or if respirators are in use. The more we learn about the way chemicals enter the body, their physical activities, and the physiological and health status of the worker to health risks of the workplace, the more we recognise the inadequacy of air monitoring and the more we appreciate biological monitoring as a powerful tool in the evaluation of chemical safety in the workplace.

The dose-effect relationship is an important concept in toxicology. In inhalation, dose is usually expressed as a product of exposed concentration and duration (Table 1) referred to as ‘external’ dose.

On the other hand the amount of chemical that has entered the body is referred to as the ‘internal’ dose. Toxic response is thus more closely related to the internal dose than the external dose.

Biological monitoring of exposure is of practical use only when the relationship between external and internal doses is known. This relationship will be discussed using a commonly commercial solvent, Trichloroethylene (TRI), as an example.

It is common knowledge that TRI is a CNS depressant and is carcinogenic in experimental animals. Neurological effects have been ascribed to exposures of TRI at concentrations as low as 100–200 ppm.

A study done by a scientific group on TRI compared the external and internal doses in a controlled environment of a worker on two separate occasions. The internal dose resulting from intermittent exposure was compared with an internal dose resulting from continuous exposure.

Continuous exposure was measured in a standard man inhaling 50 ppm of TRI for 8 hours. Intermittent exposure was measured for the same man two weeks later working in an environment where the exposure to TRI alternated between 0–100 ppm over 1 hour. The total duration for exposure in both cases was 8 hours.

During continuous exposure, the TRI concentration rose rapidly in the vessel rich tissue, slowly in muscles and very slowly in fatty tissue (Figure 1). At the end of exposure, concentration in both vessel-rich tissue and muscle approached steady state, whereas the fatty tissue still had a vast capacity to retain TRI. After exposure, the TRI concentration declined rapidly in the vessel-rich tissue, slowly in muscle and very slowly in fatty tissue. Sixteen hours after exposure the concentration in the fatty tissue was still 140 times higher than in the vessel-rich tissue.

During four hours intermittent exposure to 100 ppm, vessel-rich tissue rapidly responded to exposure changes in inhaled TRI. Muscle tissue also reflected the changes, although more slowly than in the vessel-rich tissue. However, the concentration in

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<th>External dose = level of exposure</th>
<th>Internal dose = subject concentration</th>
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<td>Airborne concentration</td>
<td>Concentration in tissues</td>
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<td>Airborne concentration x time</td>
<td>Concentration in tissue x time</td>
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<td>Time-weighted average (TWA)</td>
<td>Metabolite concentration in tissues</td>
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<td>Metabolic concentration in tissues x time</td>
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the fatty tissue rose with each intermittent exposure. It is observed that there was no real difference between the continuous and intermittent exposure in the fatty tissue after 16 hours. Intermittent exposure had little effect on urinary excretion of TRI metabolites (Figure 2).

**THE RELATIONSHIP BETWEEN EXPOSURE CONCENTRATION AND INTERNAL DOSE**

Internal doses were computed for various 8-hour exposure concentrations to trichloroethylene (Figure 3). At concentrations below 100 ppm the concentration of TRI in blood and the trichloro compounds (TCC) in urine increased almost linearly with exposure concentration.

In concentrations above 100 ppm the two measurements of internal dose e.g. TRI in blood and TTC in urine are nonlinear. The increase in TTC metabolites in urine slowed with the increased exposure concentration, while the increase in TCE in blood continued to rise.

When the exposure concentration is raised from 50–100 ppm the blood TRI concentration increased almost 40 times, whereas the cumulative amount of TTC increased only 9-fold.

This is mainly due to the saturation of the metabolite process and a rise in blood TRI concentration (Figure 4). This saturation metabolite process can be observed at exposure concentration of 400 ppm, whereas the amount of unchanged TRI in the body continues to increase with increasing exposure concentration. It must, however, be stressed that the linear relationship between exposure concentration and internal dose only exists when the exposure concentrations remain below 100 ppm.

**DURATION OF EXPOSURE**

A series of trichloroethylene exposure were studied to determine the relationship between exposure duration and dose. A worker, exposed once weekly to trichloroethylene at TWA concentration of 50 ppm for 8 hours, was used in this study. The internal dose concentration was measured over a period of 24 hours (Figure 4).

The internal dose for TRI tended to decrease as expo-

**Figure 1.** Trichloroethylene (TRI) concentration in tissue compartments and rates of trichloroacetic acid (TCA) and trichloroethanol (TCE) excretion in urine during and after an 8-hour exposure at 50 ppm trichloroethylene. VRC – vessel rich compartment; MC – muscle compartment; FC – fat compartment.

**Figure 2.** Trichloroethylene (TRI) concentration in tissue compartments and rates of trichloroacetic acid (TCA) and trichloroethanol (TCE) excretion in urine during and after four 1-hour intermittent exposure to 100 ppm of trichloroethylene. VRC – vessel rich compartment; MC – muscle compartment; FC – fat compartment.
sure duration increased. This tendency is evident from Figure 4. On the other hand, the internal dose of metabolites showed the opposite tendency; it increased with prolonged exposure. However, exceeding TWA threshold level of 400 ppm will induce a linear rise in TRI levels in the blood (Figure 3). For a TWA of 50 ppm (269 mg/m³) the BEI values by the ACGIH (2000) are 100 mg/g creatinine for trichloroacetic acid and 300 mg/g creatinine for trichloroethanol and trichloroacetic acid (end of shift and end of work week).

CONCLUSION
The TWA is a good index of an external dose for organic solvents. The same TWA concentration produces an equal internal dose provided that exposure concentrations are below a concentration at which hepatic metabolism is saturated. If the patient is exposed to a mixture of volatiles or has hepatic dysfunction the rule of equal internal dose does not apply. It is well known that some of the metabolites of volatiles are more toxic than the compound itself. The metabolites for TRI are responsible for trichloroethylene-induced hepato-toxicity and hepato-carcinogenicity. Hence the observation that prolonged exposures can be more harmful than elevated exposure concentrations.

In reality, many environmental and physiological factors alter the relationship between external and internal doses and affect the pharmacokinetic behaviour of organic solvents and cause large intra- and inter-individual differences in the results of biological monitoring.

REFERENCES

Figure 3. Internal doses were computed for various 8-hour exposure concentrations to trichloroethylene.

Figure 4. Internal dose of trichloroethylene and trichlorocomound in blood and urine respectively.

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