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Biological Monitoring IV: Measurements in Urine

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Urine is more suitable for monitoring hydrophilic chemicals, metals, and metabolites than for monitoring chemicals poorly soluble in water. The concentration of the determinant in urine usually reflects its mean plasma level during the period the urine dwells in the bladder. In some instances, however, the urine concentration is also affected by the amount of determinant stored in the kidneys. Examples are cadmium and chromium.[1]

The advantages of urine monitoring are noninvasive sampling technique, availability of sufficient volume of the sample, and requirement of relatively simple clean-up procedures. The main disadvantage is the variability of urine output which is determined by water intake and loss by the worker and which is influenced by the temperature and humidity in the workplace. Contamination during sampling can occur and can be critical for measurements of small levels of parent chemicals. Moreover, urine levels of determinants are significantly affected by the industrial environment.[2]

The accuracy of the exposure estimate using urine monitoring depends upon the sampling strategy. The most influential factors are time of collection and the urine output. To reduce the effect of urine output, the measurement of the excretion rate instead of concentration is advocated. Spot samples, representing urine output for two to four hours, are conveniently obtained and stored, and they provide a sufficiently large volume for analysis. The measurements in these specimens, collected at the identified time with respect to the exposure, usually provide good information on the intensity of the exposure. Determinant levels, however, can be affected by the length of sampling if the excretion rate changes rapidly during the sampling period. Measurements in 24-hour specimens are more representative than spot samples and usually correlate better with intensity of exposure. However, collection and transportation of these specimens are troublesome and rarely possible in the field.

The measurements can be expressed as concentration (mg/L), or they can be related to urine components, whose excretion rates fluctuate less than water excretion. Such components are total solids (measured by specific gravity) or creatinine. Measurements in specimens collected for a known period of time can also be expressed as excretion rate (mg/hr).

Renal Function

The kidney has two functions: 1) excretion of metabolic waste products, and 2) regulation of water, electrolytes, and a number of hormones and vasoactive substances. Primary anatomical units are the afferent arterioles, glomeruli, and tubules. The kidneys are perfused by approximately 1.2 L of blood per minute. Plasma flow at a rate of about 600 ml per minute carries substances via an afferent arteriole to the glomerulus. The glomerulus acts as an ultrafilter, allowing passage of electrolytes and small molecules. Approximately 20 percent of plasma water (120 ml per minute) is filtered and delivered to the tubule. Filtration of substances with a molecular weight below 5000 is unrestricted, so that their concentrations in glomerular filtrate and plasma are the same. Filtration of substances with larger molecular weight is restricted or prevented. Once a solute reaches the tubule, it is either excreted with urine or reabsorbed. Polar compounds and ions are examples of readily reabsorbed substances. On the other hand, some solids are secreted in the tubules: examples are organic acids and bases.[3] Tubular diffusion mainly facilitates elimination of exogenous substances such as some organic solvents.[4]

Renal clearance is a measure of excretion efficacy of substances. The amount of substance removed from plasma during passage through the kidney equals the amount excreted in urine. This process can be described mathematically as

$$Cl \cdot c_p = \dot{V}_u \cdot c_u \qquad (1)$$

or

$$Cl = \frac{\dot{V}_u \cdot c_u}{c_p} \qquad (2)$$

where c_p and c_u denote concentrations of the free (unbound) substance in plasma and urine, respectively; $\dot{V}_u$ is urine output per time unit; and Cl represents the volume of plasma which may be imagined to be completely cleared of the substance during a time unit. This imaginary volume per unit of time is called clearance and is expressed in volume/time units. Renal clearance of substances undergoing tubular reabsorption is relatively small and renal clearance of substances undergoing tubular secretion is relatively large.

Clearance of some determinants can be found in the literature. Measurements of clearance are not recommended for biological monitoring, but if the clearance is known, it can be used for an estimate of plasma levels when the urine levels are known and vice versa.

Chemicals and their metabolites may be excreted in a fashion similar to waste products, or they may participate with related substances in a homeostatic exchange mechanism.[5]

Chemicals and their metabolites bound to plasma proteins cannot be filtered and therefore they are excreted only after the bond is disrupted. Since only the free determinant participates in excretion, protein binding slows the excretion rate. After administration of some drugs (or other chemicals), the determinant can be re-

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leased from the protein bond on a competitive basis. As a result, an intermittent increase of determinant excretion is observed. A change in pH in urine and plasma can also affect the binding and thus alter the excretion rate.[6]

The excretion rate of chemicals and metabolites, which are *weak electrolytes,* can be markedly influenced by urinary pH. Excretion of weak acids in alkaline urine is greater than in acid urine; the converse is true for weak bases. These phenomena are largely attributed to the reduced ability of ionic forms to cross biomembranes compared to nonionized forms.

Some *volatile chemicals* such as toluene,[7] styrene,[7] methanol,[8] and nitrous oxide[9] appear to be eliminated in the kidney by a diffusion process determined by the equilibration of partial pressures in urine and plasma. As a result, the urine/blood concentration ratio equals the urine/blood distribution coefficient, and the concentration of the determinant in urine is independent from urine output.

Some *heavy metals* have a tendency to bind to metallothioneins in the renal cortex. Excretion rate of such metals is slow until the binding sites are saturated. After saturation, the metal concentration in urine suddenly increases. Cadmium excretion is an example of this saturation process.[10]

There is little information directly relating the effects of renal disease to the excretion of chemicals and their metabolites. As a practical measure, urine measurements should be used for exposure monitoring with caution, and they should be avoided for individuals with significant impairment in renal function manifested by elevated serum creatinine, diminished creatinine clearance, or proteinuria. Since the number of workers with this degree of impairment is very small, routine screening of renal function is unnecessary.

Urine Composition

Urine is the fluid excreted by the kidney, stored in the bladder, and discharged through the urethra. Urine output varies with intake and loss of fluids and with use of drugs with diuretic effects (including alcohol and caffeine). Urine consists of 90–98 percent water. The solids consist of hundreds of inorganic and organic substances, present in different amounts. In adults, the daily output of water ranges from 600 to 2500 ml (average 1200 ml), and the daily output of solids ranges from 30 to 70 g.[3, 11] With the exception of extremely diluted or concentrated urine, the excretion rate of solids, including the determinant, remains relatively constant, but the concentration of the solute grossly fluctuates depending on the urine output.[3] Therefore, measurements of determinants used in biological monitoring (with the exception of those excreted by tubular diffusion) are preferably related to excretion of solids.[12–15] In practice, this is done by adjustment of measured concentrations to a standard specific gravity. Adjustment for osmolality used in clinical laboratories is rarely used in exposure monitoring.

TABLE I. Levels of Reference Parameters in Urine of Adults (mean and range)[A]

Volume (L/day)	1.2[B] (0.6–2.5)
Solids (g/day)	50 (30–70)
Specific gravity	1.020 (1.003–1.030)
Creatinine (g/day)	1.0–1.6
(g/L)	1.0 (0.3–3.4)
pH	6.0 (4.6–8.0)

[A]The values are taken from Wallach.[11]

[B]This value corresponds to an average urine output of 0.050 L/hr.

Creatinine is a metabolic product of skeletal muscles and its excretion rate reflects the lean body mass of the subject. Its daily excretion by adults ranges from 1.0 to 1.6 g (15–25 mg/kg of body weight), the lower values being more common in women and the higher values in men.[3,11] The excretion slightly increases under physical stress. Under usual circumstances, the effect of diet, state of hydration, and diuresis on excretion rate of creatinine is relatively insignificant. Diurnal variation is minimal.[3] Therefore, measurements of determinants related to creatinine excretion are usually best correlated with the degree of exposure.[12–15] However, the adjustment for creatinine may not be justified if the excretion mechanism of the determinant is different than the excretion mechanism of creatinine. Thus, creatinine adjustment is optimal for determinants excreted primarily by glomerular filtration but is unacceptable for determinants such as nitrous oxide, methanol, and some other organic solvents which are excreted by tubular diffusion.[4]

Normalization of determinant concentration in urine. Values (mean and range) of reference urine parameters for adults are given in Table I. Equations in Table II can be used to adjust the measured concentration to the mean level of a reference parameter if levels of both the reference parameter (creatinine, density, or rate of urine output) and the determinant were measured in the same specimen.

Conversion of units of a determinant. Adjusted urine concentration can be converted into excretion rate or be related to creatinine excretion. Thus, since the mean creatinine concentration is 1 g/L, the measurement of the determinant related to the creatinine excretion (w/g of creatinine) equals the value of the concentration (w/L) adjusted to the specific gravity of 1.020. The excretion rate of the determinant is calculated using mean urine output (0.050 L/hr):

$$\text{excretion rate (w/hr)} = 0.050\ C \qquad (3)$$

where:

C = the concentration adjusted for specific gravity 1.020 (in w/L) or for creatinine excretion (in w/g of creatinine).

w = any weight unit (usually a mg or μg) and relates to the determinant.

BEI units. Since Biological Exposure Indices (BEIs) are derived for average physiological conditions, they can easily be converted into any other units. For example, the BEI for trichloroacetic acid as an in-

TABLE II. Adjustment of Determinant Concentration in Urine (w/L) to Means of Normal Values of Urine Output, Specific Gravity, or Creatinine Concentration

Concentration adjustment to:	
Urine output (L/hr)	C = vc/0.050
Specific gravity	C = 0.02c/(d-1)
Creatinine (g/L)	C = c/cr

where:

w	=	a weight unit, usually in mg
C	=	the determinant concentration adjusted to the mean level of the reference parameter
c	=	the measured concentration
v	=	measured urine output
d	=	specific gravity
cr	=	creatinine concentration

The numerical constants are derived from mean values shown in Table I. As the reference value for creatinine concentration is 1 g/L, "C" also represents adjusted concentration of determinant expressed as w/g of creatinine.

dicator of exposure to trichloroethylene is 100 mg/L.[16] It is understood that this value relates to a specific gravity of 1.020 and urine output of 50 ml/hr. By conversion, this BEI is equivalent to 100 mg of trichloroacetic acid/g of creatinine or to an excretion rate of 5 mg/hr. Conversion of units provides flexibility in biological design, giving the investigator a choice of collecting a specimen for a known period of time (i.e., to measure excretion rate) or measuring specific gravity or creatinine in spot specimens.

Some BEIs in the current *Threshold Limit Values and Biological Exposure Indices* (TLV-BEI) Booklet are expressed as concentration, excretion rate, or are related to creatinine.[16] These values are based on field measurements. After investigating numerous determinants, the BEI Committee is of the opinion that the field studies represent a relatively small number of measurements under specific conditions, and the mean values of reference parameters observed in these studies represent the studied groups rather than a general population. In the next edition of the *Documentation of the TLVs and BEIs*, BEIs will be given only as concentrations adjusted to creatinine excretion. If necessary, the user can convert the BEI into another unit, using the conversion equation as described above. BEIs will, however, be specified for other units if the need is indicated by the excretion mechanism of the determinant.

Sampling, Storage, Analysis

Proper timing of the specimen collection and the possibility of contamination are the main concern. Tampering with the sample is possible. Relating determinants to density or creatinine is a means of spotting tampering of a specimen by dilution with water.

The excretion mechanism of determinants can be altered when the urine specimen is very concentrated (specific gravity > 1.030, creatinine > 3 g/L) or dilute (specific gravity < 1.010, creatinine < 0.5 g/L). In this case, measurements in urine samples are not reliable and should be repeated in a specimen collected on some other occasion.

To collect specimens for measurements of excretion rates, the worker is asked to empty the bladder and record the exact time. This should be done approximately three hours before the end of the shift when the BEI is available for the "end of shift specimen." The worker is then provided with a 500 ml container (a jar with a wide opening and screw top lid) in which the next voiding of urine is quantitatively collected. The time of the final collection is recorded. To obtain the urine output, the total volume of urine collected in the container is measured and divided by the total elapsed time during which the urine was collected.

The spot urine specimen should be collected at the time indicated in the BEI Documentation.[1,16] Measurement of creatinine concentration or specific gravity should be requested in the same sample as measurement of the determinant concentration. Creatinine is measured in urine by a colorimetric method, known as the Jaffe reaction, which is based on an intense red color following reaction with alkaline picrate.[17] Most clinical laboratories can perform analyses on automated equipment for relatively low cost. Results are usually accurate to ± 10 percent. Specific gravity can be read directly on the scale of a densitometer (urinometer) dipped in the urine. The measurement must be made in fresh urine because the solids, once sedimented, cannot be properly restored in the solution. The equations for adjustment of determinant concentration to the reference value of creatinine concentration or specific gravity is shown in Table II. For measurements of determinants which can be easily biased by contamination of a sample in the working environment, showering and changing clothes prior to sampling is advisable.

Specimens for measurements of volatile determinants should be collected in a 50-ml container which must be completely filled with the specimen and immediately sealed in order to prevent losses in the head space and to the environment. In some instances, urine can be collected in containers of known volume and the measurement of determinant concentration in the head space can be used for calculation of determinant concentration in urine.[4] The samples for this analytical technique must be kept sealed in containers which can endure overpressure caused by changes of temperature during transportation and storage.

Urine samples usually deteriorate more slowly than blood samples; refrigerated storage is recommended. Samples which require long-term storage (more than five days) should be kept frozen. Before aliquots are taken for analysis, the samples must be well mixed. When selecting the analytical method for urine, the same consideration must be given to binding and conjugation of determinant as described for blood analysis.[18]

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