Biological monitoring for isocyanates

Analysis of urine to assess exposure to Isocyanates
Guidance for workers, employers, and occupational health professionals

What is the problem with isocyanates?
Isocyanates cause asthma. They are the biggest cause of work-related asthma in the UK. Not everyone working with isocyanates gets asthma but HSE is concerned that there are too many workers get asthma each year. People with asthma caused by isocyanates have to change jobs to protect their health. Exposure to isocyanates must be well controlled. The controls must be checked to make sure they are working.

Why analyse urine?
If isocyanates are inhaled they are metabolised or broken down in the body and eliminated in urine. The level of isocyanate metabolites in urine is an indicator of how much isocyanate has been absorbed and how well the controls are working.

In some jobs, like spraying 2-pack paints, control relies on air-fed masks and measurement of isocyanate metabolites is a simple way of checking that the mask fits, works and is used properly.

Is it compulsory?
No. Giving a urine sample is voluntary but it is in everyone’s interest to make sure that worker’s health is being protected by good control of exposure. In some cases (like paint spraying) it may be very difficult to check by any other way that the controls are working.

How should samples be collected?
Collecting samples of urine to assess exposure is usually called biological monitoring. HSE has produce guidance booklets on how to set up a biological monitoring programme. Briefly, everyone needs to know:

- why samples are being collected (to check exposure to isocyanates),
- when they should be collected (at the end of exposure),
- how often (once or twice a year unless results show there is a problem),
- What will be measured (isocyanate metabolites only not drugs or alcohol etc)
- Who will see the results (it makes most sense if the workers let management see the results so they can work together to sort out any problems)
- What happens if the results show controls are not working as well as they should (try and find out why, sort it and then check again)

Someone needs to manage the process and usually this would be the occupational health provider (workers using isocyanates are required to have health surveillance). An occupational hygienist or a manager could also manage the programme perhaps with initial help from an occupational physician.

An important aspect is that the worker(s) understand what is being done and why (i.e. they can give informed consent).
Samples are collected into 30ml plastic bottles containing 0.5g of citric acid. The bottles should be firmly closed and labelled with the worker’s name, and date of collection.

Samples should be sent to the laboratory by first class post (or equivalent) in appropriate packaging (usually supplied by the laboratory) with details of the tests required (isocyanate) and where to send the results.

**What do the results mean?**

The laboratory will report the results something like this:

<table>
<thead>
<tr>
<th>Name</th>
<th>HDA µmol/mol creatinine</th>
<th>TDA µmol/mol creatinine</th>
<th>IPDA µmol/mol creatinine</th>
<th>MDA µmol/mol creatinine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mr Smith</td>
<td>2</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Guidance</td>
<td>1</td>
<td>1</td>
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<td>1</td>
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</tbody>
</table>

HDA is hexamethylendiamine the metabolite of hexamethylenediisocyanate (HDI)
TDA is toluenediamine the metabolite of toluenediisocyanate (TDI)
IPDA is isophoronediamine the metabolite of isophoronediisocyanate (IPDI)
MDA is methylenedianililine the metabolite of methylenediphenyl diisocyanate (MDI)

The levels of HDA, TDA etc are reported as ‘µmol/mol creatinine’. Creatinine is found in everyone’s urine and can be used to adjust the level of HDA, TDA etc to compensate for dilute or concentrated urine.

The guidance value is 1 and in the example above for TDA, IPDA and MDA the level (<1) is less than the guidance value showing either no exposure or well-controlled exposure. For HDA, the level reported above is 2 and is above the guidance value.

**What do I do if I have a result above the guidance value?**

If a biological monitoring result is above the guidance value it may mean that the methods of controlling exposure to isocyanates are not working as well as they should. If the result is the first from a worker then it is sensible to ask for another sample for confirmation. It is also sensible to investigate how the worker may be exposed to isocyanates and whether the controls are working as intended.

It should be noted that because the guidance value is based on the value found in 9 out of 10 samples in places with good control it is likely that 1 in 10 values will be above the guidance value even in places with good control.

**Will anything else be measured?**

No – the laboratory will not analyse the urine sample for anything else.

**How often should monitoring be done?**

The frequency of monitoring should be related to the adequacy of controls. If results are below the guidance value, sampling may be as infrequent as once per year unless working practices change or new workers are employed. If the results exceed the guidance value, a repeat sample should be taken. If this sample is also positive, the reasons should be investigated and further samples should be taken after implementing changes to improve control of exposure. Sampling should be repeated until results are below the guidance value.
1) Biological Monitoring in the workplace A guide to its practical application to chemical exposure HSE 167
2) 2) Biological Monitoring in the workplace Information for employees on its application to chemical exposure HSE books INDG245 (free)
BIOLOGICAL MONITORING for ISOCYANATES
Technical Guidance on laboratory methods

Biological Monitoring Guidance value:
1 µmol isocyanate derived diamine/mol creatinine in urine collected at the end of exposure.

Method for Isocyanated derived amines in Urine

☐ **Sample Collection**
When: Collect urine samples at the end of exposure – the urinary half-life is around 2 hours and results reflect exposure over the previous 2 – 4 hours.
How: Collect samples in a polystyrene universal container (30ml) containing 0.5g citric acid and close the container securely to prevent leaks.

☐ **Sample Transport to laboratory**
Send samples by first class post (or equivalent) to arrive within 48h of collection. If any delay anticipated, store at –20°C. Packaging must comply with Post Office regulations.

☐ **Description of Suggested Analytical Method**
Add internal standards (100 µl of heptane diamine 1µM and ethylenedianiline 5µM) to urine (2 ml). Acidified with concentrated sulphuric acid (200 µl). Cap the tubes and incubate at 100 °C for 90 min. After cooling add sodium hydroxide (2ml, 10M) and diethyl ether (4ml) and mix for 20 min. Centrifuge and remove 3ml of each ether layer to a clean tube and remove the solvent under nitrogen. Derivatise the residue with heptafluorobutyric anhydride (50 µl) in toluene (500 µl) in closed tubes at 55°C for 1h. Cool and remove the derivatising reagent under nitrogen and reconstitute in toluene (100µl). Inject (1µl) splitless (350°C, 30 sec) into a capillary column (30m x 0.3 mm BP5 1µm) at 150 °C increasing at 10 °C/min to 240 °C then 20 °C/min to 300 °C. Detect by mass spectrometry with negative ion chemical ionization (methane) monitoring ions at m/z 488, 449, 462, 495 and 542 from 4 to 10 min and m/z 571 and 585 from 11 to 15 min.

☐ **Analytical Evaluation**
Precision
- within day <5% RSD at 200 nmol/l
- day to day <12% RSD at 200 nmol/l
Detection limit
- 3 x background - 1 nmol/l (approximately 0.1 µmol/mol creatinine)
Limit of Quantitation
- 5 x LoD – 5 nmol/l (approximately 0.5 µmol/mol creatinine)
Calibration range
- typically 50 - 300 nmol/l
Sample Stability
-2 days at ambient, > 3 months at –20 °C
Analytical interferences
-None known

☐ **Other Information**
Elimination half-time
- The half-life for HDI and TDI is around 2 hours so the previous days exposure will not affect the results. The half-life for MDI is much longer (over 50 hours has been reported for repeated exposures) and so previous days’ exposures will influence results.

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Confounding Factors
Exposure to free hexamethylene diamine, toluenediamine, isophoronediamine and methylene dianiline will also contribute to their respective urinary diamine levels and may confound assessment of exposure to the isocyanates. A pre-exposure sample for MDI may help in these cases

Unexposed Levels
< 0.5 µmol /mol creatinine

Quality Assurance
- Internal QC must be established.
- External QA - available from HSL

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