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## Analysis of Plasticizers in Medical Products by GC-MS with a Combined Thermodesorption - Cooled Injection System

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### **KEYWORDS**

Direct Thermal Desorption, GC-MS, Plasticizer, Di-2-ethylhexylphthalate (DEHP), 4-Heptanone, 2-Heptanone, Cyclohexanone

## **ABSTRACT**

The combination of a new thermodesorption module with a cooled injection system (TDS-2,CIS-3, Gerstel, Mülheim, Germany) now provides a powerful thermodesorption system for direct analysis of volatile trace compounds in gaseous, liquid and solid samples. As a cooled injection system is used for the cryofocusing of the desorbed volatiles the GC-MS system still can be used for the regular analysis of liquid samples. Plasticizers can usually be analyzed by liquid extraction with alcohol/water, but special care has to be applied not to use contaminated solvents. Direct analysis of plastics by thermal desorption saves time and avoids cross contaminations. Many containers for intravenous solutions are made with plasticized polyvinyl chloride, the common form of which is di-2-ethyl hexyl phthalate (DEHP). Extraction of DEHP into blood and plasma stored in such plastic containers can occur, and harmful effects of DEHP in the human body consequently have been suggested. We therefore analyzed 30 plastic tubings which are used for various invasive techniques in medicine.

## **INTRODUCTION**

DEHP has been a priority pollutant for several years because of its large quantities emitted and its widespread use and occurrence in the environment [1-15]. Polyvinylchloride (PVC) has replaced the older rigid plastics in most of the medical applications. PVC is made flexible by interfusing various plasticizers containing phthalic acid esters such as DEHP, which may constitute up to 40% of the finished plastic in medical products. In addition to the plasticizers antioxidants, catalysts, inhibitors and heat stabilizers are frequently added to the plastic. The softer and more pliable the plastic, the higher content of plasticizer found will more readily leach into the liquids passing through it. This is particularly true for lipid containing fluids like blood.

There have been reports of extraction of DEHP from plastic intravenous infusion sets [6, 14] into certain infusates and finally into the human body. Patients undergoing hemodialysis are exposed to DEHP via contact of blood with tubings containing DEHP [11-14]. There is great concern about the toxicity of DEHP and its metabolites [8, 10, 12] especially for risk groups such as patients on hemodialysis or critically ill patients, where DEHP was detected in plasma. Some of the proposed and shown effects are carcinogenicity, peroxisome proliferation, mutagenic activity, infertility (toxic effect on Sertoli cells) and changes in lipid metabolism [8, 15]. But almost all of the tests have been done in animal studies with metabolism different from humans.

Different metabolites have been blamed for the toxicity: phthalic, mono- and di-reesterified phthalate, 4- and 2-heptanone and 2-ethylhexanol [1-3, 7, 8, 10]. After hydrolysis 2-ethyl hexanol may

be further oxidized to 2-ethyl hexanoic acid, which itself can undergo  $\beta$ -oxidation to yield two isomeric  $\beta$ -oxo-acids. Spontaneously and upon heating these acids would give rise to the two isomeric ketones 2-heptanone and 4-heptanone.

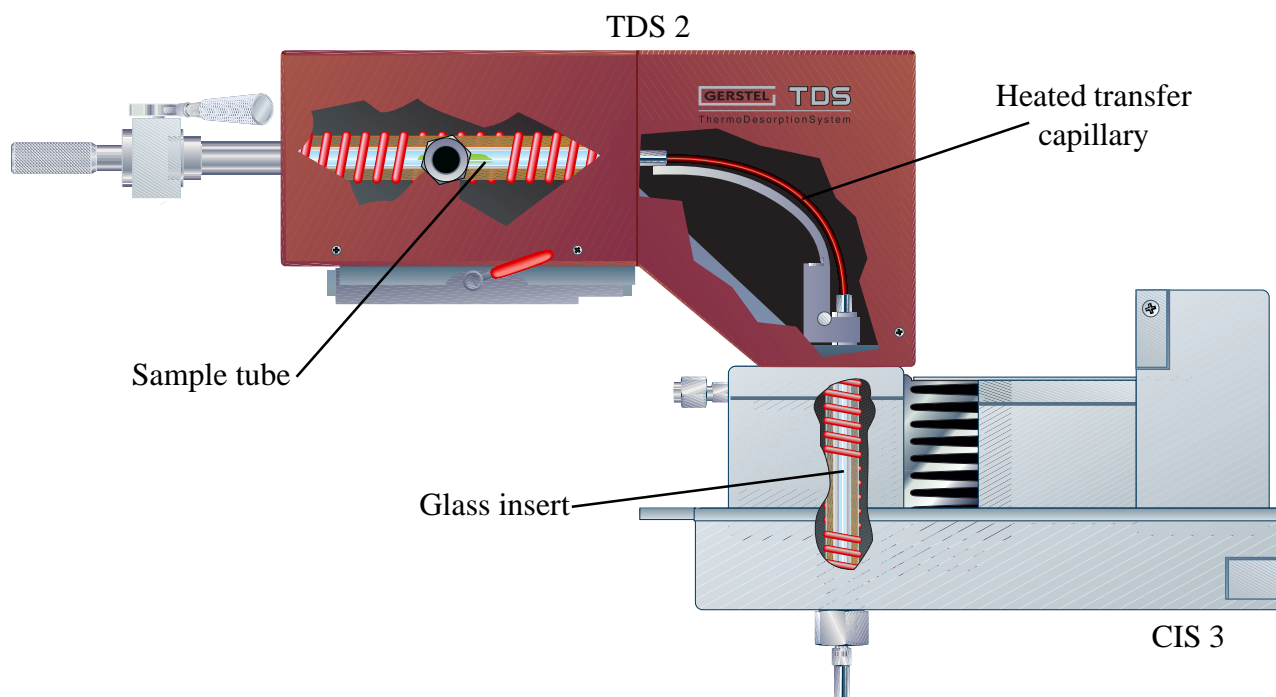
Elevated levels of 4-heptanone and 2-heptanone in urine and serum from patients on hemodialysis and diabetic patients were reported earlier [16-19]. Since we also found high concentrations in dialysis patients and from patients in our intensive care unit, we investigated the medical tubings used in our clinic.

The standard analysis procedure for plasticizers would be solvent extraction and subsequent GC or GC-MS identification. The major problem is the use of solvents which themselves are very often contaminated with plasticizers. The method of direct thermal desorption on the other hand is easy to perform and free of contamination as no solvents are introduced.

## EXPERIMENTAL

*Sample preparation.* Small portions (10 mg) of the plastic under investigation were placed in a clean empty glass thermal desorption tube.

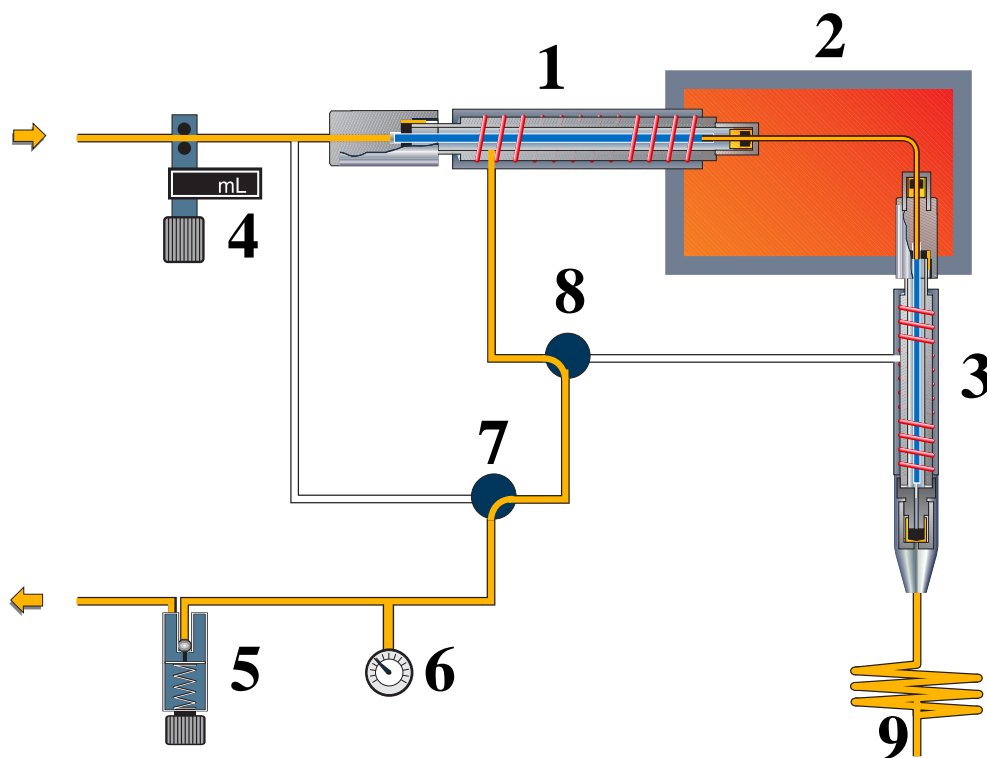
*Instrumentation.* The system consists of a thermodesorption system (TDS 2, Gerstel GmbH, Mülheim an der Ruhr, Germany, **Figure 1**), a temperature programmable cooled injection system (CIS 3, Gerstel GmbH, Mülheim an der Ruhr, Germany, **Figure 1**), a gas chromatograph HP 6890, and a mass selective detector HP 5972 (both Hewlett-Packard, Waldbronn, Germany).



**Figure 1.** Thermodesorption system TDS 2 attached to CIS 3.

*Operation.* A blank glass tube is filled with the sample and then inserted into the TDS desorption chamber which is cooled down to ambient temperatures in order to prevent premature desorption. After purging the air out of the system, the tube is then heated to the 120°C, while the carrier gas flowing through the tube transfers the volatiles in splitless-mode (**Figure 2**) into the pre-cooled CIS, where they are cryofocused and concentrated.

After the desorption has finished the CIS is heated to 280°C to allow split- or splitless transfer of the trapped compounds to the analytical column and further mass spectrometric detection.



**Figure 2.** Schematic of the applied system which consists of a thermodesorption system (1), a temperature controlled transfer capillary (2), a cooled injection system (3), standard backpressure pneumatics with mass-flow controller (4), backpressure regulator (5), pressure gauge (6) and split/splitless valve (7), including an additional 3/2-way solenoid (8) to switch the splitflow between TDS and CIS. The analytical column (9) is directly connected to a mass selective detector.

*Analysis conditions.*

Column: 60 m DB 5 (J&W)  $d_i = 0.25 \text{ mm}$   $d_f = 0.25 \text{ }\mu\text{m}$   
Pneumatics: Carriergas He, constant flow mode (1 ml/min)  
split 1:100  
Temperatures: TDS 20°C; with 60°C/min to 300°C (5 min)  
CIS -150°C; with 12°C/s to 300°C (3 min)  
Oven 50°C (1 min); with 10°C/min to 300°C (10 min)  
MSD 300°C  
MSD: Scan, 35-350 amu

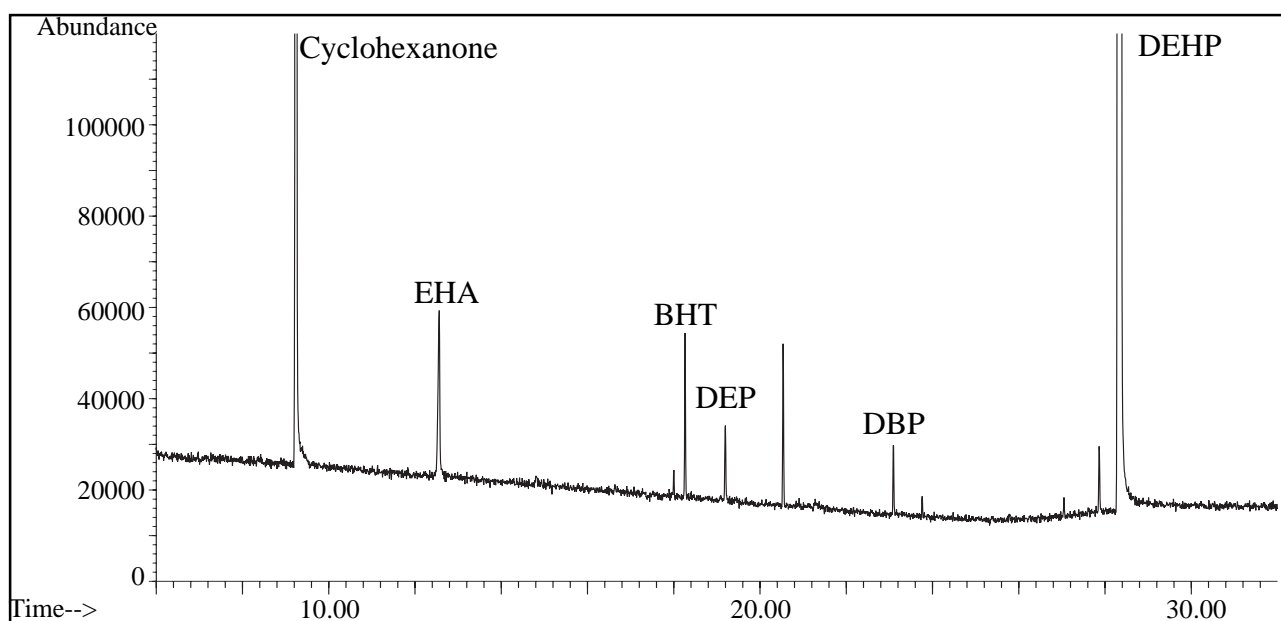
## RESULTS AND DISCUSSION

Depending on the nature of the plastic different plasticizer and solvents were found. In some of the plastic up to 30 different components were found (**Table I**). By far the most common plasticizer found was DEHP, followed by diethyl- and dibutyl phthalate.

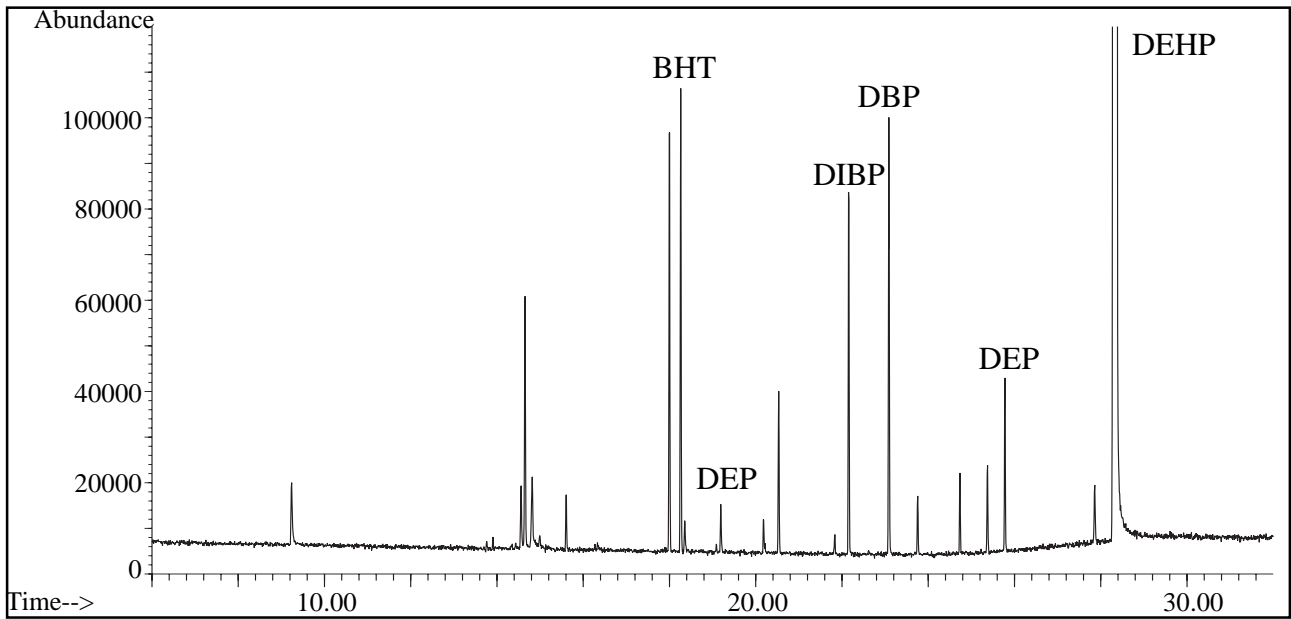
| Volatiles  | RT (min) | Volatiles                                 | RT (min) |
|--|----------|---|----------|
| Cyclohexane  | 6.1      | Hexadecane                                | 19.0     |
| Toluene  | 7.1      | Diethyl phthalate (DEP)                   | 19.1     |
| 2,4-Dimethyl heptane   | 8.0      | Heptadecane                               | 20.1     |
| 2,4-Dimethyl-1-heptene   | 8.3      | 4,4'-Dichloro-1-1'-biphenyl               | 20.6     |
| Xylene   | 8.7      | Octadecene                                | 21.2     |
| Styrene  | 9.1      | Octadecane                                | 21.3     |
| Cyclohexanone  | 9.3      | Di isobutyl phthalate (DIBP)              | 22.2     |
| Decane   | 10.8     | Hexadecanoic acid                         | 22.8     |
| 2-Ethyl hexanoic acid (2EHA)                                       | 12.5     | Dibutyl phthalate (DBP)                   | 23.0     |
| Benzoic acid   | 13.4     | Eicosane                                  | 23.3     |
| Dodecane   | 13.9     | Butyl-2-ethyl hexyl phthalate (BEP)       | 25.7     |
| Caprolactame   | 14.7     | Hexanedioic acid bis(2-ethyl hexyl) ester | 26.9     |
| Tetradecane  | 16.6     | Di (2-ethyl hexyl) phthalate (DEHP)       | 28.2     |
| Dimethyl phthalate   | 17.4     |   |          |
| Pentadecane  | 17.8     |   |          |
| 2,4-bis(1,1-Dimethyl ethyl)-phenol butylated Hydroxy toluene (BHT) | 18.2     |   |          |

**Table I.** Peak identification.

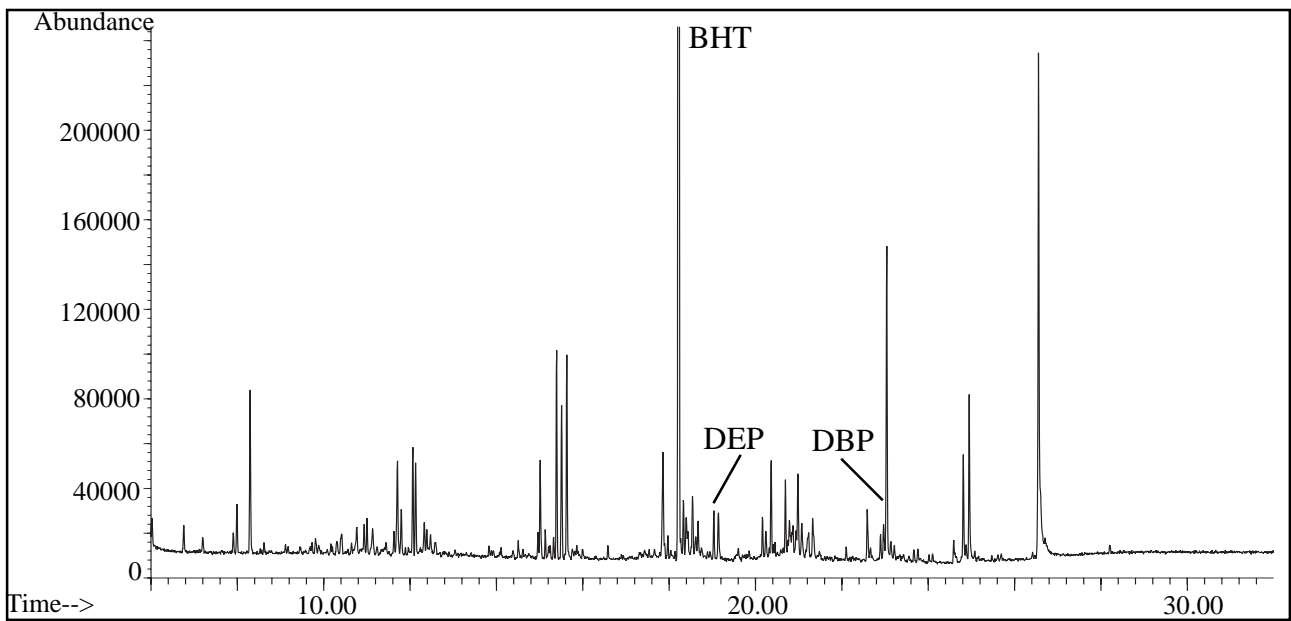
In a few dialysis tubings we found cyclohexanone, a volatile we have found to be elevated in the urine of dialysis patients and other patients in our clinic. **Figure 3** shows a chromatogram of a dialysis tubing, **figure 4** an infusion set, **figure 5** a syringe used for subcutaneous injections of insulin and **figure 6** a syringe used for subcutaneous injections of heparin.



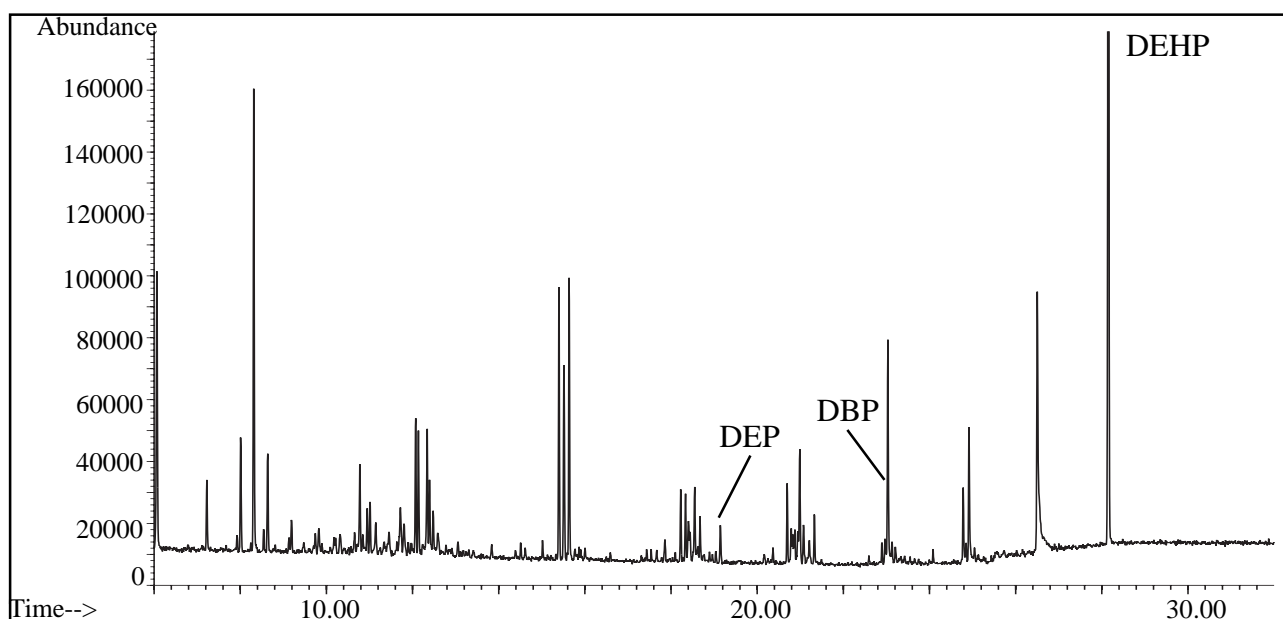
**Figure 3.** Chromatogram of a dialysis tubing.



**Figure 4.** Chromatogram of an infusion set.



**Figure 5.** Chromatogram of a syringe used for subcutaneous insulin injections.



**Figure 6.** Chromatogram of a syringe used for subcutaneous heparin injections.

From the 34 different plastic articles analyzed (**Table II**) phthalates were found mainly in soft pliable PVC plastics used for invasive applications. Pipette tips and rigid plastic containers used for urine collection or storage of other liquids, often made of polypropylene, did not contain DEHP. Instead a variety of alkanes, alkenes and BHT were found in large amounts and to a lesser extent DEP and DBP.

| Plastic article          | DEP | DIBP | DBP | BEP | DEHP |
|--------------------------|-----|------|-----|-----|------|
| Eppendorf pipette tips   | X   |      | (X) |     |      |
| Eppendorf cup            | (X) |      | (X) |     |      |
| Urine container, 100 ml  | (X) |      | (X) |     |      |
| Urine container, 500 ml  | (X) |      | (X) |     |      |
| Urine container, 2500 ml | (X) |      | (X) |     |      |
| Urine bag, 1500 ml       | (X) |      | (X) |     | X    |
| Syringe, 60 ml           | (X) |      | (X) |     | (X)  |
| Insulin syringe          | (X) |      | (X) |     |      |
| Heparin syringe          | (X) |      | (X) |     | X    |
| Microfilter, 40 $\mu$ l  | X   |      | X   | (X) | X    |
| Serum monovette          | (X) |      | (X) |     |      |
| Butterfly                | X   |      |     | X   | X    |
| Luerlock obturator       | (X) |      | (X) |     | X    |
| Infusion tubings         | (X) | X    | X   | X   | XX   |
| Infusion bag             | (X) |      | X   | (X) | XX   |
| Blood storage bag        |     |      |     |     | XX   |
| Blood infusion tubings   | (X) |      | (X) | X   | XX   |
| Intestinal tubings       | X   |      | X   |     | X    |
| Dialysis tubings         | (X) |      | (X) |     | XX   |

**Table II.** Phthalate contents in medical plastic articles.

## CONCLUSIONS

The metabolic pathway of DEHP in vivo is hydrolyzation to 2-ethylhexanol and oxidation to the corresponding  $\beta$ -keto-acid excreted in urine. Spontaneously and upon heating this acid yields 4-heptanone and 2-heptanone. All major intermediates have been found and identified in serum, urine and breath. First results from human studies under current investigations show the plasticizer DEHP to be the origin of elevated 4-heptanone as well as 2-heptanone concentrations in urine and plasma of patients on hemodialysis or in the intensive care units.

DEHP was found mainly in soft pliable PVC plastics used for invasive applications and blood storage bags, but not in rigid plastic containers. Extraction of DEHP from plastic intravenous infusion sets into the human body occurs and should therefore be monitored, especially in risk groups such as patients on hemodialysis or critically ill patients. Metabolism studies of DEHP as well as investigations concerning the toxicity require the analysis of DEHP and other additives in the original plastic article. The standard analysis procedure for plasticizers would be solvent extraction and subsequent GC or GC-MS identification. The major problem hereby is the use of solvents which themselves are very often contaminated with plasticizers.

The direct thermal desorption method for plasticizers described here is a convenient way to identify plasticizers and other components of medical plastic tubings without contaminations as no solvents are introduced.

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