Assessment of the absorbed dose after exposure to surgical smoke in an operating room

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Conflict interest
The authors have no competing interests for this study.

ABSTRACT

Surgical smoke produced by electrosurgery contains various chemical substances such as volatile organic compounds (VOCs) and polycyclic aromatic hydrocarbons (PAHs). The aim of this study is to investigate airborne concentrations of VOCs and PAHs during electrosurgery in an operating room, in relation to metabolites in urine in order to assess the absorbed dose.

A 5-day exposure study was set up in a general surgery operation room including surgeons, scrub assistants and circulation nurses (n=15). Stationary and personal air sampling for VOCs and PAHs were carried out. Pre-, mid- and end-shift analysis of urinary S-phenylmercapturic acid (SPMA), o-cresol, mandelic acid and 1-hydroxypyrene was performed to assess the internal exposure to respectively benzene, toluene, styrene and PAHs.

Several VOCs (styrene, ethyl benzene, benzene and toluene), ranging from 0.7 to 3.27 µg/m^3 were detected in the air samples, along with one PAH (naphthalene, ranging from 0.012 to 0.39 µg/m^3). There was no significant correlation between air monitoring and urinary biomonitoring. O-cresol levels were increased, especially among assistants and nurses at mid- and end-shift, exceeding current biological exposure indices several times. External and internal exposure for assistants and nurses was substantially more, compared to surgeons.

This study confirms the presence of VOCs and PAHs in surgical smoke and shows the presence of their metabolites in urine, but the association is unclear. Urinary biomonitoring shows especially high concentrations of o-cresol.

KEYWORDS: diathermy plume, diathermy smoke, electrosurgery, healthcare workers, occupational exposure, electrocautery, electrocoagulation, VOC, PAH, biomonitoring

INTRODUCTION

Electrocautery is one of the most commonly used techniques in the operating room during surgery. Concerns about the generated surgical smoke have existed for years but there is still no consensus on the associated potential health risks (1–3). Surgical smoke consists out of 95% water vapour and 5% combustion by-products and cellular waste. Smoke quantity and its by-products composition may vary based on the surgeon's technique, the target tissue, type of energy transferred, power levels used and the degree of coagulation or cutting (1,4,5)**.**

Surgical smoke consists out of various chemicals including PAHs, VOCs, CO, acrylonitrile, HCN and formaldehyde (1–3,6). Some studies indicate that the airborne concentrations may exceed occupational limit values (1,4,7). Benzene concentrations can rise up to 0,16 - 2,32 ppm in the operating theatre. Other studies showed a predominance of a mixture of naphthalene, toluene and benzene in surgical smoke (8,9). Moot *et al* conclude that the exposure levels to VOCs in surgical smoke can be compared to second-hand cigarette smoke (10). In general, also a wide diversity of PAHs is found in surgical smoke, with naphthalene as the most abundantly present (1,11).

Surgeons have an intermittent exposure to high concentrations of surgical smoke. Mostly, nurses are exposed to much lower concentrations, yet they are more continuously exposed (5,8,12,13). The influence of type of surgery, such as open or laparoscopic surgery, on surgical smoke has not been investigated.

Although the airborne exposure of surgical smoke has been investigated thoroughly already, the assessment of the absorbed dose through biomonitoring has not yet been investigated. Yet, this would give more accurate information about the actual potential health risk of surgical smoke, since it determines the actual entrance of chemicals into the body.

The health risks of exposure to surgical smoke are determined mainly by the toxic effects of the individual chemicals. For example, benzene and butadiene are classified by the International Agency for Research on Cancer (IARC) as Group 1

and naphthalene and other PAHs as Group 2B carcinogens. Yet, individual chemicals can have a synergistic or antagonistic effect on each other, so changing the toxic effect of a particular substance (11)**.** Moreover, a low but continuous exposure to surgical smoke raises concern based on a potentially long-term cumulative effect (5,8,12), leading to the assumption that dangers of surgical smoke are relevant for everyone who enters an operating room (10)**.** As found in literature, a standard surgical mask does not protect against VOCs and PAHs, while local exhaust ventilation (LEV) can completely eliminate these compounds (4,9).

The aim of this study is to determine internal exposure to surgical smoke in an operating room in relation to external exposure. We focused on the quantitative analysis of VOCs and PAHs through stationary and personal air sampling and urinary metabolites of benzene, toluene, styrene and PAHs. The rationale for this selection is based on the availability of relevant associated biomarkers for a non-invasive sampling technique and the availability of a standardized, quantitative and validated analysis technique in the selected laboratory.

METHODS

This study was conducted in a general surgery operating room at a hospital in Antwerp, Belgium, between September and November 2018. The study was approved by the Ethical Committee of the University Hospital of Antwerp and by the Ethical Committee of the general hospital where the study was executed (No. 375). Because we were unable to identify other studies published on the biomonitoring of surgical smoke exposed operating room personnel, it was not feasible to calculate the minimum sample size required for the current study. This study serves as a pilot for further research.

Operating room and surgical procedures

Sampling was performed daily during five consecutive days, each time in the same operating room, in a general surgeon, the scrub nurse and a circulation nurse. During the surgical procedures no local portable smoke evacuation units were used. The surgical site was disinfected with Iso-Betadine Hydroalcohol before incision. Scrub personnel wearing standard surgical masks used DAX Alcoliquid Pro as disinfectant during scrubbing. Two independent researchers recorded the characteristics of each surgical procedure and collected information on demographic characteristics, last exposure to surgical smoke, medical history and diet during the last 24 hours of participants.

The operating room is equipped with an independent circuit for germ-free air supply. This is achieved by HEPA filtration based on a three-step method whereby a suction filter and a secondary filter are placed opposite the end filter. The air is supplied through a perforated panel in the wall and extracted through 4 perforated panels in the opposite wall (Figure 1). This creates a horizontal laminar airflow at the surgical site. Air changes in the room exceed 30 cycles per hour. Overpressure is created to limit the spread of germs into the operating room.

Air sampling

Personal active air sampling was performed at the breathing zones of the subjects. One stationary active air sampling was placed out at the top right grid (Figure 1B) of

the general exhaust. The sampling took place during every surgical procedure of one work shift (8h). This procedure was repeated for each of the five sampling days.
Given the large number of different chemical substances present in surgical smoke, this study was limited to VOCs and PAHs. For the measurements of the VOCs, a 400/200mg Active Carbon tube (SKC 226-09, Lot 2000) was used. For the PAHs a Teflon filter (Millipore LSWP02500, 5 µm pore size) mounted in a 25 mm IOM cassette, and a XAD-2 tube (100 mg front section, 50 mg back section; Supelco 20258) were connected in series. Both collection media were connected with a pump (SKC Ltd, Dorset UK), with a flow rate of 1 L/min and were calibrated before and after each sampling day. Normally, the IOM samples is designed to collect the inhalable fraction, by sampling at 2 L/min, but in series with an XAD-2 tube, 1 L/min is more recommended. It is assumed that this lower flow rate does not influence the collection of particles with an aerodynamic diameter smaller than 30 microns. The personal measurements were performed in the breathing zone of the participants. The IOM/XAD-2 sampling train was attached at the collar of the participants. The samples were appropriately labelled, stored and delivered within 24 hours to the laboratory.

Quantitative analysis of VOCs

Air samples were pre-treated according to methods earlier described (14–16). Briefly, the front and back section of the charcoal tubes were separately extracted with carbon disulfide (purity >99.9%, Honeywell 342270, VWR International, Leuven, Belgium). Analysis was performed by gas chromatography with double flame ionization detection (Agilent 7890B GC). Analysis was simultaneously performed on two capillary columns (split-mode) with different polarity, according to an in-house developed and extensively validated method, based on different analytical methods as published by the National Institute for Occupational Safety and Health. An aliquot of 2 µl of the sample was injected on a SPB-1, 60 m, 0.32 mm i.d., 1.0 µm film thickness column (apolar) and on a WAX10, 60 m, 0.32 mm i.d., 0.5 µm film thickness column (polar). Detection by flame ionization was performed at a temperature of 250 ˚C. Each sample was assayed systematically for 187 different compounds, including hydrocarbons, chlorinated compounds, alcohols, ketones, ethers, esters, glycol ethers and others. The different compounds were identified on

the basis of a unique set of two relative retention times while quantification was based on a compound-specific relative response factor. An in-house made computer program allowed rapid, automated data-processing of the obtained GC chromatograms. Upon interlaboratory comparison tests, the used single-run analytical GC method provided highly reproducible and accurate results of airborne VOC concentrations, with analytical precision generally <3% and global measurement uncertainty generally <10%. For the calculation of the air concentration, the compound-specific desorption-efficiency, as well as the measuring time and sample air volume were also considered.

Quantitative analysis of PAHs

Analysis of 16 EPA (Environmental Protection Agency) polycyclic aromatic hydrocarbons was performed according to an in-house developed and validated method, based on NIOSH method 5515. Briefly, the 25 mm teflon filter and both sections of the XAD-2 tube were each chemically extracted with 1 mL of methylene chloride, containing biphenyl as internal standard (10 µg/mL). A gas chromatographic analysis is performed with mass spectrometric detection (GC-MS) on an Agilent 6890 GC, 5973 MSD. An aliquot of 5 µl is splitless injected on a DB5-MS capillary column (30 m length, 0.25 mm internal diameter, 0.1 µm film thickness). The chromatographic separation was obtained using a temperature program with an initial oven temperature of 60°C, increased at a rate of 10°C/min to a final temperature of 280°C. Each sample was assayed systematically for the presence or absence of 16 different PAHs: acenaphthene, acenaphthylene, anthracene, benz[a]anthracene, benzo[b]fluorantene, benzo[k]fluorantene, benzo[ghi]perylene, benzo[a]pyrene, chrysene, dibenz[a,h]anthracene, phenanthrene, fluoranthene, fluorene, indeno[1,2,3-cd]pyrene, naphthalene and pyrene. Identification of the PAHs present in the sample was performed based on the retention time and presence of specific tracer ions in the mass spectrum. Quantification of the different PAHs was performed by using the abundance of these tracer ions. A calibration solution series of the different PAHs was prepared, starting from a certified PAH standard (Supelco 48905-U, 2000 µg/mL of each PAH in methylene chloride: benzene (1:1)). The calibration series were prepared at 3 different concentration

levels: 0.1 µg/ml, 0.5 µg/ml and 1 µg/ml. The quantification limit for all different PAHs is situated below 0.01 µg/ml.
The air concentrations of the VOCs and PAHs will be compared to the Belgian recommended limit values and to the 2018 TLVs of the American Conference of Governmental Industrial Hygienists (ACGIH).

Urinary biomonitoring

Analysis of urinary S-phenylmercapturic acid (SPMA), o-cresol, mandelic acid and 1-hydroxypyrene was performed for the biomonitoring of respectively benzene, toluene, styrene and PAHs.

Pre-shift urine samples were taken around 8:00h, mid-shift urine samples around 12:30h and end-shift urine samples around 16:30h. Mid- and end-shift urinary sampling was performed 30min to 2h after the cessation of smoke production. Smoke exposure between pre- and mid-shift samples was of a longer duration than between mid- and end-shift due to the lunch break after mid-shift sampling. These samples were put in vacuum containers, appropriately labelled, and immediately placed in cool (-5°C) storage. These specimens were delivered to the laboratory within 24 hours where they were frozen at -80°C.

Quantitative analysis of biomarkers

Quantitative analysis of creatinine, 1-hydroxypyrene, SPMA, o-cresol and mandelic acid was performed for every urine sample according to standing procedure in the Laboratory of Occupational and Environmental Hygiene of the KU Leuven in Belgium.
Creatinine analysis was performed according to Jaffe method. Quantitative determination of 1-hydroxypyrene was done following the method published by Miao *et al*, (17). Briefly, urine samples (10 ml each) were subjected to an enzymatic hydrolysis for 1 h, and then 1-OHP was extracted using C18 cartridges. Urine samples were then analyzed with an Agilent 1290 series Ultra-high-performance liquid chromatography system coupled to fluorescence.

Urinary SPMA was determined using a LC-MS/MS methodology as described by Scheepers *et al,* (18): 1 mL of the urine was transferred into a new test tube and spiked with 50 µL of the internal standard (10 µg/mL) S-PMA-d5 and acidified with 10 µL of hydrochloric acid (6N) and 940 µL of aqueous formic acid (1 %, pH 7). After a purification step using a simplified liquid extraction (SLE) column, the solution was dried out with a nitrogen stream at 40-50°C. Next, 50 µL acetonitrile/water (20:80) as added as solvent and the tube was vortexed. 10 µL of this final mixture was injected into the ultraperformance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) (Xevo TQ-XS Triple Quadrupole Mass Spectrometer (Waters, Zellik, Belgium) for analysis.

The analysis of urinary mandelic acid was performed according the method published by Creta *et al* (14): 0.1 mL of centrifuged urine was acidified with 10 µL of HCl 6 N and diluted with 0.9 mL of MilliQ water containing 10 µg/mL of 4-hydroxybenzoic acid (4-HBA) as internal standard. The urine samples were then extracted with 3 mL of ethyl acetate; after extraction, 1 mL of the organic layer was pipetted in a test tube and dried out under a gentle nitrogen stream. The samples were reconstituted in a 3 mL water-methanol mixture (90:10, v/v) and 10 µL of the resulting solution was injected on a UPLC-MS/MS instrument (Waters Acquity Ultra-Performance Liquid Chromatograph equipped with Xevo TQ-XS Tandem Quadrupole Mass Spectrometer).

O-cresol in urine was determined on aliquots (5 mL) of urine samples loaded onto capped tubes. One mL of concentrated hydrochloric acid was added to all tubes and incubated for 90 minutes at 95ºC in the hydrolysis step. After incubation, tubes were let to cool at room temperature. Nitrobenzene working solution (100 µL) was added as internal standard and mixed vigorously with a vortex. A salting out was performed adding 1g of solid sodium chloride. Two mL of diethyl ether was added as extraction solvent and mixed in vortex for two minutes. The organic layer was placed into clean vials containing anhydride sodium sulphate to eliminate the possible humid present. Once the extracts were dehydrated they were placed into vials for injection on a Hewlett Packard 5890 gas chromatograph coupled to a Flame ionization detector.

The urinary concentrations of mandelic acid and o-cresol were given in mg/l, of SPMA in ng/ml and of 1-hydroxypyrene in µg/l urine. The concentrations were converted into mg/g creatinine or µg/g creatinine according to the units of the corresponding Biological Exposure Indices (BEI) by using the given creatinine concentrations (mg/dl) in order to compare them to the BEIs proposed by of the American Conference of Governmental Industrial Hygienists (ACGIH) and adapted by Lauwerys and Hoet (19). The BEI of PAHs could be calculated using the equation introducing a correction factor corresponding to the ratio of the airborne concentration of the sum of benzo(a)pyrene equivalents to pyrene (19).

Statistical analysis

The data of air sampling and biomonitoring was converted to continuous variables. For non-detectable values $1/10^{th}$ of the detection limit was used. Symmetry of the distributions was assessed by using a histogram. Because of the skewness of the data, the median and interquartile ranges were estimated.

Daily trends of metabolites were recorded and plotted in graphs while trends within the different occupations of health workers were shown using boxplots for the different working shifts. Correlations of personal air monitoring and biomonitoring were calculated using Spearman's rank correlation. Since mandelic acid is the metabolite of styrene as well as of ethyl benzene, both chemicals were considered to determine this correlation.

Given the limited number of observations data analysis was only performed in a descriptive way, no inferential statistics were used. All analysis was done using R version 3.5.

RESULTS

Social and demographic variables

In total 10 persons were included in this study of which 3 surgeons, 2 scrub assistants and 5 nurses. Some of them participated more than once depending upon the medical staffing on the sampling days, declaring n=15. Their characteristics are displayed in supplementary table S1. The characteristics of the surgeries performed are displayed in a supplementary file (Table S2). On day 1 only open surgeries were performed, on the other days a mix of open and laparoscopic.

Air sampling

A detailed list of all identified VOCs and PAHs during stationary and personal air monitoring with their measured concentrations and limit values are shown in the supplement (Table S3 and S4). Due to a technical error there is no data of stationary PAHS air sampling on day 2 available.

No concentrations of the chemicals exceeded the Belgian or ACGIH limit values. Identified chemicals with potential health hazards were ethanol, iso-propanol, diethyl ether, methyl ethyl ketone, benzene, hexane, toluene, ethyl benzene, xylene and others. In all cases ethanol was the most common VOC. Most PAHs were undetectable. Only from time to time a limited increase of naphthalene was detected and this did not exceed the individual TLVs of all substances. Since, we have identified a mixure of chemicals, the Belgian legislation, along with the ACGIH recommends to use the summation formula for a full shift analysis: $C1/T1 + C2/T2 + C3/T3 + Cx/Tx \leq 1$ (were C is the concentration and T the TLV of the compound). For both personal and stationary measurements these calculated values were far below 1. This is the case for time weighted average (TLV-TWA) and short-term exposure limits (TLV-STEL). This means that exposure via the respiratory tract is far below any limit value.

Table 1 shows the median values for styrene, ethyl benzene, benzene, toluene and naphthalene. The scrub assistant had the highest exposure to toluene and naphthalene, the circulation nurse to styrene, ethyl benzene and benzene.

Urinary biomonitoring

Urine was collected pre-, mid- and end-shift. The concentrations of the metabolites were compared to the BEIs that can be found in the supplement (Table S5). Table 2 shows the median and interquartile range for all metabolites analysed (see also Figure S1, data represented as boxplots).

Low concentrations of mandelic acid were found in the urine of the surgeons with no differences between pre-, mid- and end-shift. For the scrub assistants pre-shift concentrations were somewhat increased than those at mid-shift. Both were higher compared to those of the surgeons. End-shift concentrations were substantially higher compared to both surgeons and circulation nurses. The circulation nurses had pre- and mid-shift values comparable to those of the scrub assistants. They had pre-shift values that were higher than mid-shift as well as the scrub assistants. End-shift concentrations of the circulation nurses were comparable to those of the surgeons. Pre-shift mandelic acid values exceeded the reference value for non-occupationally exposed persons two times in the group of the circulation nurses (Table 5S). Mid- and end-shift values never exceeded the BEI.

Pre-shift concentrations of o-cresol in the urine of the surgeons were around the detection limit. Higher values were detected in mid-shift samples with a further increase at end-shift. However, compared to the scrub assistants and circulation nurses the concentrations of the surgeons were low. Increased o-cresol was found in the group of the scrub assistants both mid- and end-shift. The mid-shift value did not further increase at end-shift. At the level of the circulation nurses a decline in concentration between pre- and mid-shift and an increase between mid- and end-shift were identified. Pre-shift values of o-cresol exceeded the reference value twice, once at the level of the scrub assistants and once at the level of the circulation nurses. At mid-shift the BEI was exceeded five times, once at the level of the surgeons and four times at the level of the scrub assistants. End-shift values exceeded the BEI six times, two times at the level of the scrub assistants and four times at the level of the circulation nurses.

SPMA urinary concentrations of the surgeons were similar at pre- and mid-shift and substantially increased at end-shift. With regards to the scrub assistants pre- and end-shift concentrations were comparable to the pre-shift concentrations of the surgeons except for a decline at mid-shift. Concentrations in the group of the circulation nurses were substantially higher than those of the surgeons and scrub assistants, but there were no differences between shifts. SPMA concentrations in the urine samples never exceeded the reference value or BEI.

All urinary 1-hyroxypyrene concentrations were below the detection limit in the group of the surgeons except for one low detectable end-shift value. At the level of the scrub assistants most concentrations were below the detection limit except for one mid-shift and two end-shift measurements. They were low and comparable to the surgeon's detectable value. For the circulation nurses, all values were below the detection limit except for one end-shift measurement. This concentration was substantially higher than all others. Since pyrene and benzo(a)pyrene were not found it was not possible to calculate the BEI for 1-hydroxypyrene.

Correlations between personal air monitoring and urinary biomonitoring

A Spearman's rank correlation test was performed to correlate all concentrations of chemicals found by personal air sampling and corresponding end-shift urinary metabolites. We found no correlation between benzene air exposure and SPMA in urine end-shift ($r=0.22$). Neither for toluene and o-cresol ($r=0.28$), for styrene plus ethyl benzene and mandelic acid ($r=0.25$) nor for naphthalene and 1-hydroxypyrene ($r=-0.28$) a correlation was found.

DISCUSSION

We wanted to investigate the concentrations of airborne VOCs and PAHs exposure during electrocautery and to investigate whether biomonitoring for benzene, toluene, styrene and PAHs could detect exceedance of internal exposure of the BEIs (19). Rather low air concentrations of VOCs and PAHs were detected, yet some urinary metabolites were remarkably high, with substantial variabilities among tasks. The BEI of o-cresol was exceeded several times, but there were no correlations between air and urinary samples. Exposure for scrub assistants and circulation nurses was higher compared to surgeons.

Personal and stationary air sampling showed the presence of multiple VOCs, among others, benzene, styrene, toluene, and several alcohols, and only one PAH, being naphthalene. This is in accordance with the results of Barrett *et al* (1). The health effects of these chemicals are well known. Yet, all concentrations we measured were in the µg/m³, so far below any limit values for occupational exposure.

The low air exposures did only partially correlate with the urinary metabolites that were identified. In some cases, workplace exposure was well reflected in increased concentrations found in mid- and end-shift urine vs pre-shift urine, but this was mostly not the case. For example, the pre-shift exceedance of the reference value for non-occupational exposed persons of o-cresol in samples from the nurse can probably be attributed to smoking habits or exposure to disinfectants. Moreover, for o-cresol the mid- and end-shift values exceeded the BEI 6 times on the level of the scrub assistant, 4 times on the level of the circulation nurse and once on the level of the surgeon.

Each attendee in the operating room has his specific task, with substantial difference in exposure. The scrub assistant was mainly exposed to toluene and naphthalene, while the circulation nurse was mainly to styrene, ethyl benzene and benzene. This is reflected in the urinary metabolites of the scrub assistant, who had the highest median mid- and end-shift concentrations for o-cresol. The exposure for scrub assistants and circulation nurses seemed to be more substantial compared to surgeons. This could be explained by the fact that the surgeon stayed shorter in the

operating room compared to the scrub assistant who closed the wounds and performed administrative tasks in the OR and compared to the circulation nurse who prepared before and cleaned up after surgery. The distance to the source of fume production seemed to be of less influence, since the circulation nurse with the longest distance to it seemed to have more exposure than the surgeon who was closest.

We found no correlation between air sampling and biomonitoring. Neither air sampling nor biomonitoring provides us with the exact level of exposure. Probably, we have underestimated the air exposure, because we had to interrupt the air sampling after each surgery. It was practically not possible for the operating room workers to wear the pumps all day. In parallel, the stationary air sampling was also stopped for the same period. Yet, the concentrations found in the air were in the µg/m³ range and it is unlikely that the unsampled time would substantially increase the concentrations of the noxious agents. Another reason could be that some chemicals are dermally absorbed and so influence the values of the biomonitoring. Since we did not assess skin exposure, we cannot make any statements concerning this issue.

As we sampled the volunteers each day, both in the morning, at midday and after the full shift, we have individual time trends for biomonitoring (data not shown). Mostly, the urinary metabolites were not detectable. Therefore, we could not find any associations with these time trends. Since all of the chemicals for which we did biomonitoring, were detected by air sampling, one would expect that the trends of the metabolites would have been similar. Yet, this is not the case. This can be explained by the following reasons. 1/ Differences in chemical composition can be found in surgical smoke depending on the target tissue of the coagulation (1,3,4). For example, coagulation of skin releases more toluene than coagulation of fat tissue (2). Smoke generated from the cauterization of epidermal tissue was found to contain higher levels of toluene, ethylbenzene, and xylene, while smoke generated from the cauterization of adipose tissue contained lower levels of toluene and greater levels of aldehydes (2,5). 2/ The half-lives of the measured metabolites are substantially different. SPMA has a half-life of 9h. Increased concentrations of SPMA

pre-shift might therefore be attributable to exposure that happened the day before. O-cresol on the other hand has a rapid initial elimination (<5h), followed by a minor second phase which can go up to 40h. This initial fast elimination is also reflected in our results, with substantially increased o-cresol levels at mid-shift time points. The third metabolite mandelic acid has a biphasic half-life (5h and 20h). This biphasic behaviour can explain the few high pre-shift concentrations of mandelic acid reflecting exposure of the day before. While the end-shift increase in mandelic acid reflects the exposure of the same day. 1-hydroxypyrene has a quite long half-life of approximately 18h. So, there could be a lot of interference of previous shifts and smoking habits on the results. (19). Therefore, if biomonitoring is considered to assess exposure to surgical smoke, it is very important to know the composition of the smoke first in order to define the correct moment to collect urine. Additionally, according to Lee *et al* variation in duration of exposure to surgical smoke might also result in differences in results (9). 3/ Other contributors heavily influence the urinary concentration of the metabolites, such as smoking, alcohol use, application of medical disinfectants, etc (19). In this study the scrub assistant disinfected the whole surgical field before each surgery and used extra disinfectant at the end of the surgery to clean the wound edges after closing, potentially raising the levels of o-cresol. 4/ Biomonitoring is also influenced by interindividual differences in metabolization rates. We found less variability in the pre-shift concentrations compared to the mid- and end-shift values (Table 2 and Figure S1). This corresponds to the conclusion of Cheng *et al* (3) that metabolization depends on toxicokinetics (rate and type) and match between profiles. Since some metabolites increased during the shift indicates that there was an exposure to potentially dangerous chemicals. Yet, a study on a larger scale needs to be conducted to further investigate this hypothesis.

Our study has some important limitations such as the number of samples collected in this study was relatively small potentially triggering a wide variation in the results. Moreover, since the number of samples is so limited, we decided not to exclude the smoker from the analysis, which could influence the data. Yet, we did not find any indication for this. By assessing pre-, mid- and end-shift urinary metabolites insights of individual kinetics of metabolites in different persons were obtained. With regards

to the air sampling it would have been better to interrupt the air sampling only mid-shift so it coincides better with the biomonitoring at mid-shift. Another limitation of the study is that the pre-shift values were compared to reference values for a non-occupational exposed population instead of taking a control group within the hospital. For statistical analysis, 1/10th of the detection limit was used for non-detectable values of the biomonitoring. This may give distorted results, especially when all of the values of one day are below the detection limit. This is especially the case when urine is very diluted. When calculating the concentrations of the metabolites into g/g creatinine it is possible that with low creatinine urine levels higher values for non-detects are obtained. Furthermore, some chemicals are also dermally absorbed and hereby influencing the values of the biomonitoring. Future studies could include dermal sampling of these chemicals.

To conclude, this study confirms that very low concentrations of VOCs and PAHs are present in surgical smoke produced by electrosurgery. O-cresol was found to be elevated, but this could not be clearly linked to toluene exposure from surgical smoke in operating room personnel. Circulation nurses and scrub assistants seem to be more exposed to surgical smoke than surgeons. Yet, further research should be performed to further determine the specificity and selectivity of o-cresol, overall and in different surgeries performed.

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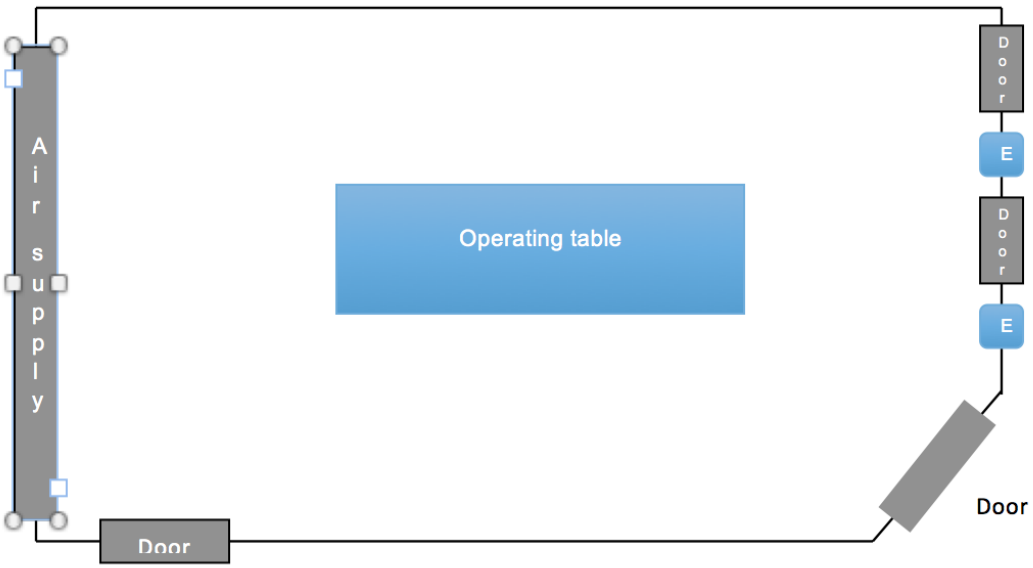
FIGURES

A.



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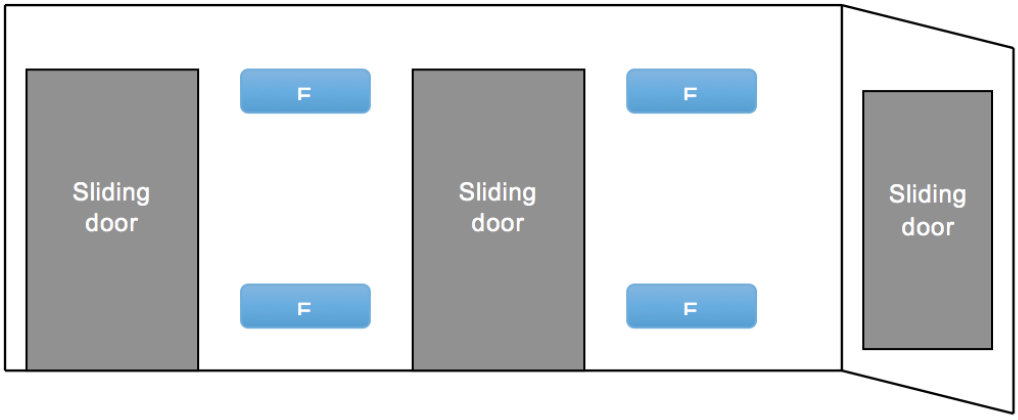

Figure 1: setup of the operating room. A is a helicopter view of the operating room; B is a view of the opposite wall with four perforated panels for air extraction. E = air extraction

TABLES

Table 1: Median (IQR) concentrations detected by stationary and personal air sampling

	Stationary air monitoring *(n=14-15)*[1]	**Personal air monitoring**			
		All tasks (n=15)	*Surgeon (n=5)*	*Scrub assistant (n=5)*	*Circulation nurse (n=5)*
Styrene (µg/m^3)	2.660 (2.28-3.27)	2.75 (2.215-3.25)	2.75 (2.22-2.98)	2.74 (2.26-3.29)	3.1 (2.21-3.21)
Ethyl benzene (µg/m^3)	0.83 (0.7-1.02)	0.86 (0.685-1.015)	0.86 (0.68-0.93)	0.86 (0.69-1.03)	0.97 (0.69-1.0)
Benzene (µg/m^3)	0.83 (0.7-1.02)	0.86 (0.685-1.015)	0.86 (0.68-0.93)	0.86 (0.69-1.03)	0.97 (0.69-1.0)
Toluene (µg/m^3)	0.83 (0.7-1.02)	0.93 (0.69-4.45)	0.86 (0.68-0.93)	3.1 (0.86-5.8)	0.97 (0.69-9.2)
Naphthalene (µg/m^3)	0.036 (0.012-0.167)	0.16 (0.010-0.39)	0.24 (0.16-0.33)	0.3 (0.017-0.71)	0.016 (0.004-0.065)

IQR = inter quartile range. [1]Due to a technical error, there was no data for the stationary sampling of PAHs (naphthalene) on day 2.

Table 2: Median (IQR) urinary concentrations per task.

	Pre-shift n=5	**Mid-shift** n=5	**End-shift** n=5	**Reference value[1]**	**BEI[2]**
Mandelic acid (mg/g creat)					
Surgeon	0.229 (0.208-0.309)	0.25 (0.169-0.266)	0.118 (0.115-0.139)	ND	300
Scrub assistant	1.389 (1.136-1.667)	0.676 (0.455-0714)	1.79 (1.55-11.46)		
Circulation nurse	1.25 (0.208-3.49)	0.439 (0.287-1.19)	0.25 (0.238-0.718)		
o-Cresol (mg/g creat)					
Surgeon	0.01 (0.01-0.01)	0.01 (0.01-0.07)	0.09 (0.08-0.19)	0,1 (non-smokers) - 0,3 (smokers)	0,3
Scrub assistant	0.1 (0.07-0.13)	0.54 (0.19-0.58)	0.44 (0.26-0.46)		
Circulation nurse	0.15 (0.05-0.27)	0.05 (0.01-0.53)	0.2 (0.01-0.38)		
SPMA (µg/g creat)					
Surgeon	0.007 (0.001-0.013)	0.006 (0.001-0.009)	0.012 (0.01-0.016)	5	25
Scrub assistant	0.007 (0.006-0.007)	0.003 (0.003-0.007)	0.007 (0.001-0.011)		
Circulation nurse	0.013 (0.009-0.02)	0.015 (0.008-0.015)	0.015 (0.012-0.021)		
1-HP (µg/g creat)					
Surgeon	0.0018 (0.0017-0.0019)	0.0016 (0.0014-0.002)	0.0011 (0.0009-0.0014)	NA[3]	NA[3]
Scrub assistant	0.0111 (0.0091-0.0133)	0.0057 (0.0054-0.013)	0.0029 (0.002-0.013)		
Circulation nurse	0.0018 (0.0017-0.0027)	0.0023 (0.0018-0.0035)	0.002 (0.0019-0.02)		

[1]Pre-shift values were compared to reference values for non-occupationally exposed subjects (12). [2]Mid- and end-shift values were compared to the biological exposure indices (BEI) (12). [3]It was not possible to calculate the reference value or BEI for 1-hydroxypyrene since pyrene and benzo(a)pyrene were always below detection limit. ND=not detectable, NA=not applicable