

# Occupational exposure to sevoflurane following topical application to painful wounds

DÁMASO FERNÁNDEZ-GINÉS<sup>1</sup>, CARMEN SELVA-SEVILLA<sup>2</sup>, MANUEL CORTIÑAS-SÁENZ<sup>3</sup>,  
MANUEL GERÓNIMO-PARDO<sup>4</sup>

<sup>1</sup> Department of Pharmacy, Torrecárdenas Hospital, Almería

<sup>2</sup> Faculty of Economics, University of Castilla La Mancha, Spain

<sup>3</sup> Pain Management Unit, Department of Anesthesiology, Torrecárdenas Hospital, Almería

<sup>4</sup> Department of Anesthesiology, Complejo Hospitalario Universitario de Albacete

**KEY WORDS:** Air pollution; occupational exposure; painful wounds; topical administration of drugs; topical sevoflurane

**PAROLE CHIAVE:** Inquinamento dell'aria; esposizione occupazionale; ferite dolorose; applicazione topica di medicinali; uso topico di sevoflurano

## SUMMARY

**Background:** Occupational exposure to halogenated anesthetics employed for general anesthesia has been extensively studied. Conversely, a new modality of treatment of painful wounds with topical sevoflurane lacks exposure studies.

**Objectives:** To evaluate the magnitude of acute occupational exposure to sevoflurane following topical application to painful wounds. **Methods:** Four patients with chronic painful wounds were treated with topical sevoflurane (20, 20, 20 and 10 mL) following an approved therapeutic protocol in our Pain Management Unit. Eight passive dosimeters were placed at different locations of a treatment room with a volume of 163 m<sup>3</sup> and 3.3 air changes per hour: 3 for near peak (for 20–50 min) and 1 overall exposure (for 3.4 h) at the nurse's breathing zone, and 4 for area exposure (for 3–3.4 h). Worst-case scenario theoretical concentrations of sevoflurane were also calculated. **Results:** The highest levels were obtained for two dosimeters worn by the nurse at the breathing zone (8.28 and 9.12 ppm-TWA [parts per million-Time-Weighted Average]), while the lowest level was obtained from the dosimeter placed on the most distant wall from patients (0.73 ppm-TWA). Theoretical concentrations were calculated from standard volatilization principles and were in agreement with the concentrations measured. **Discussion-Conclusions:** All air concentrations measured were lower than exposure limits set by occupational safety agencies from Finland, Sweden and Norway, which range from 10 ppm for a TWA of 8 hours to 20 ppm for short-term exposures (15 min). Application of topical sevoflurane on wounds seems to be environmentally safe for health-care professionals as it produces exposure levels lower than the established limits for anesthetic procedures.

## RIASSUNTO

«**Esposizione occupazionale a sevoflurano durante l'applicazione topica per il trattamento di ferite dolorose**». **Introduzione:** L'esposizione occupazionale a anestetici alogenati utilizzati per l'anestesia generale è stata ampiamente studiata. Al contrario, mancano ancora studi di valutazione dell'esposizione per la nuova modalità di trattamento

Pervenuto il 5.4.2019 - Revisione pervenuta il 2.9.2019 - Accettato il 10.9.2019

Corrispondenza: Manuel Gerónimo Pardo, MD, PhD, Department of Anesthesiology, Complejo Hospitalario Universitario de Albacete, Spain - E-mail: sergepu@hotmail.com

**Previous presentation:** This work was presented in part as a communication at the Spanish Wound Meeting (Congreso de la Sociedad Española de Heridas - SEHER 2019), which was held in Madrid, Spain, in February 2019.

delle ferite dolorose attraverso somministrazione topica di sevoflurano. **Obiettivi:** Valutare l'entità dell'esposizione occupazionale acuta al sevoflurano durante applicazione topica per il trattamento di ferite dolorose. **Metodi:** Quattro pazienti con ferite dolorose croniche sono stati trattati con sevoflurano (20, 20, 20 and 10 mL) applicato direttamente sulla ferita seguendo un protocollo terapeutico approvato nella nostra Unità di Terapia del Dolore. Otto campionatori passivi sono stati posizionati in punti diversi di un ambulatorio con un volume di 163 m<sup>3</sup> e 3.3 ricambi di aria/ora: quattro campionatori sono stati collocati nella zona respiratoria dell'infermiere, 3 per 20–50 min, ovvero per la durata del trattamento di ciascun paziente e 1 per 3.4 h, ovvero la durata complessiva dell'esposizione. Quattro campionatori sono stati posizionati in centro ambiente per una durata di 3–3.4 ore. Sono state anche calcolate, utilizzando un modello, le concentrazioni teoriche di sevoflurano nell'ipotesi di esposizione peggiore. **Risultati:** I livelli più alti sono stati ottenuti per due dosimetri indossati dall'infermiere (8.28 e 9.12 ppm-TWA [parti per milione, come valore medio ponderato nel tempo]), mentre il livello più basso è stato misurato dal dosimetro posizionato sulla parete più lontana rispetto ai pazienti (0.73 ppm-TWA). Le concentrazioni teoriche calcolate sono risultate concordi con le concentrazioni misurate. **Conclusioni:** Tutte le concentrazioni aeree misurate erano inferiori ai limiti di esposizione fissati dalle agenzie per la sicurezza sul lavoro di Finlandia, Svezia e Norvegia, che oscillano da 10 ppm per una TWA di 8 ore a 20 ppm per esposizioni brevi (15 min). L'applicazione topica di sevoflurano sulle ferite sembra essere sicura per il personale sanitario perché produce livelli di esposizione inferiori a quelli stabiliti per le procedure di anestesia.

## INTRODUCTION

Sevoflurane is a fluorinated ether derivative which is widely employed to perform general anesthesia. It is presented as a nonflammable clear colorless liquid, but its volatility (vapor pressure of 157 mmHg, boiling point of 58.6°C) allows for it to be administered by inhalation (4). Even though modern anesthetic machines have gas extraction systems to reduce environmental pollution in the workplace and room air is renovated at very high rates, it is nearly impossible to get healthcare professionals completely free from anesthetic gas exposure (27). But, although environmental exposure is a matter of concern, regulatory aspects are still very poorly developed. In the USA the National Institute for Occupational Safety and Health (NIOSH) is still working to establish a specific limit for sevoflurane (30), and most European countries lack specific regulation (24), included Spain (13). It is noteworthy that limits are not uniformly regulated among the few countries regulating sevoflurane so far (24), as Nordic European countries exemplify (31). Even in neighboring countries, limits for sevoflurane range from 5 parts per million (ppm) in Denmark (3) to 20 ppm in Norway (1), while Finland and Sweden share two limits: one of 10 ppm for long-term exposure (considered as 8h-working day) and also a limit of 20 ppm for short-term exposure (considered as 15 minutes) (17, 18).

Recently, several groups have communicated their experience irrigating chronic painful wounds with neat sevoflurane. All literature reports have confirmed a rapid, robust and long-lasting analgesic effect (12, 22). In addition, antimicrobial and healing effects have also been described in some clinical cases (10, 12, 26). As a result, topical administration is becoming a new off-label indication for sevoflurane; in fact, this new modality is currently used at several hospitals in Spain. Direct wound irrigation with liquid sevoflurane is expected to produce an occupational exposure pattern essentially different from that of general anesthesia, but this subject has not been studied.

The primary goal of this pilot study was to evaluate the occupational exposure associated with the application of topical sevoflurane to chronic painful wounds.

## METHODS

### Ethical statement

Patients were treated with topical sevoflurane strictly following the usual therapeutic protocol previously approved by our local Institutional Review Board (IRB), for which they previously gave written informed consent. In addition, to perform this specific research on environmental levels of sevoflurane

a slight modification was made to the aforementioned protocol, which was also authorized by our local IRB. Since the aim of this research was measuring sevoflurane air concentrations without introducing any other modification over the approved therapeutic protocol, we were exempted by our IRB from asking patients for formal informed consent – though the patients were aware of the research.

### Therapeutic protocol

As stated above, the authors' Pain Management Unit (PMU) has currently a protocol for ambulatory treatment with topical sevoflurane for patients suffering from chronic painful wounds. Patients referred to the PMU who accept to be included in such protocol have to give written consent. At inclusion, a first cleansing of the wound is performed, using topical sevoflurane as preemptive analgesic agent. Then patients or relatives are given sevoflurane prefilled syringes for home self-administration, which usually last one or two months, so that they come to the Unit on a monthly/bimonthly basis to get more syringes. The wounds are then cleansed in a procedure room during this scheduled visit.

The routine procedure followed by cleansing of the wounds consists in removing the bandage, bathing the wound bed with saline and soapy sponges, irrigating with liquid sevoflurane at an approximately dose of 1 mL/cm<sup>2</sup>, and covering it with a gauze. After waiting for 5 minutes, painless mechanical debridement is performed, sevoflurane is again applied to provide postprocedure analgesia, and a new bandage is put in place. Used gauzes and bandages are discarded into an open medical waste trash can.

Sevoflurane is presented as 250 mL opaque bottles (Sevorane™, AbbVie, Campoverde di Aprilia, Italy). By protocol, opaque 10 mL syringes with hermetic cap (BD Plastipak™, Madrid, Spain) are filled with sevoflurane in a vertical laminar flow cabinet in the Pharmacy Department, and then provided for topical use.

### Experiment

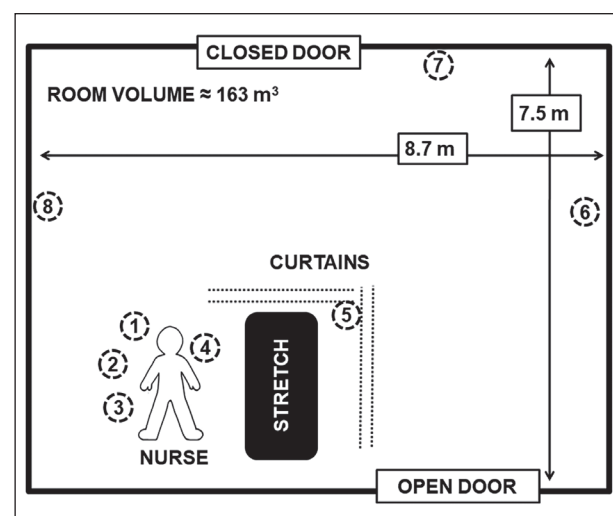
The procedure room is approximately 163 m<sup>3</sup> in volume. There are no windows but two doors, and

only one of them can be opened (figure 1). Room air is renewed 3.3 times per hour with fresh air without recirculation.

The day the study was performed the temperature ranged between 22 and 24°C and relative humidity between 45 and 65%. That evening four patients suffering from venous chronic painful wounds (18, 16, 21 and 6 cm<sup>2</sup> in size) were treated with sevoflurane (20, 20, 20 and 10 mL, respectively) following the above described protocol.

Air samples were collected using passive dosimeters (VAPOR TRAK™ Waste anesthetic gas monitors, Kem Medical Products Corp., Farmingdale, New York, USA) with a low limit of detection of 0.02 ppm and an overall system accuracy for sevoflurane of ±7.23%.

Five dosimeters remained in place from the start of the treatment of the second patient to the end of the fourth: one on the nurse's left side of the gown (breathing zone), another one on the curtains half-surrounding the stretcher, and three on the walls. Other three dosimeters were sequentially put in place on the same nurse's right side of the gown (again breathing zone) since they only remained for the duration of every single debridement (figure 1). Exposure time for every dosimeter was recorded, which was defined as the period of time elapsed be-



**Figure 1** - Schematic representation of the treatment room of the Pain Management Unit where debridements were performed. Numbered circles identify the position of the eight dosimeters

tween their opening and later their hermetical sealing. There was only a single nurse who carried all personal dosimeters and took care for the wounds, including sevoflurane application.

After using them, dosimeters were sent for analysis to a reference laboratory (Kem Medical Products Corp, Fort Lauderdale, Florida, USA). Briefly, sevoflurane from a badge exposed for a known time is extracted and analyzed by gas chromatography-flame ionization detection to obtain a mass (mg). Then, the mass (mg) is converted to exposure level (ppm.hrs) using a standard curve. Finally, the exposure level is converted to a Time-Weighted Average for the sampling time. The procedure is based on Occupational Safety and Health Administration (OSHA) method #103 (25). Results for sevoflurane measurements were expressed in two ways: as absolute amount of sevoflurane, in  $\mu\text{g}$ , and as parts per million - Time Weighted Average (ppm-TWA).

### Sevoflurane exposure simulation

A model of sevoflurane vapor concentrations in the procedure room with a two-phase steady-state-logarithmic decay was used to predict potential worst-case scenario concentrations of the volatile substance according to standard volatilization principles as described previously elsewhere with a few modifications (11).

The following underlying assumptions were used:

- Sevoflurane diffusion throughout the procedure room was instantaneous.

- There was no absorption of sevoflurane by the patient (or all absorbed sevoflurane was exhaled without changes).

- The first phase represents the steady-state concentration, which is reached and maintained while the entire volume of sevoflurane applied topically (20 or 10 mL) evaporates in a closed space. It was considered to start just after sevoflurane application and to last until its complete evaporation (estimated to be 20 minutes).

- The second phase started just after the end of the first phase, once the liquid has evaporated completely. The concentration of sevoflurane can no longer be sustained and begins to decline exponentially. During this phase, subsequent vapor concen-

trations were calculated according to exponential decay, which is governed exclusively by the ventilation rate.

- For repeated administration (a new patient was treated every 50 min), the concentration vapor at any given time step is the sum of the vapor remaining after decay of the most recent treatment plus the steady state concentration ( $C_{ss}$ ) of the subsequent treatment.

Evaporation rate (E) was calculated as:

$$(1) E = \frac{\text{Mass used for wound irrigation}}{\text{Effective usage time}}$$

Effective usage time was assumed to be 1 hour, which corresponded to the administration frequency of each dose.

The steady state concentrations ( $C_{ss}$ ;  $\text{mg}/\text{m}^3$ ) were maintained over a 20 min evaporation time, and were:

$$(2) C_{ss} = \frac{E}{V/n}$$

Where V is the volume of the room ( $163 \text{ m}^3$ ), and n is the number of air changes per hour (3.3 ACH).

Steady state concentrations measured in mass ( $C_{ss}$ ;  $\text{mg}/\text{m}^3$ ) were converted into concentrations measured in parts per million (ppm), assuming  $25^\circ\text{C}$ , standard pressure, and molecular weight of sevoflurane of  $200 \text{ g}/\text{mol}$ :

$$(3) C_{ss}(\text{ppm}) = \frac{C_{ss}(\frac{\text{mg}}{\text{m}^3}) * 24.45}{\text{Molecular weight}}$$

Once the evaporation ceases, the concentration of vapor was calculated according to the equation:

$$(4) C_t = C_0 * e^{-nt}$$

Where  $C_t$  is the concentration in ppm at time t in hours following the evaporation phase,  $C_0$  is the  $C_{ss}$  at the last time point of the evaporation phase, n is the number of ACH, and t are the time points (every minute) following the evaporation phase.

Finally, air concentrations from the evaporation and decay phases of all applications at each time point were added to calculate the time weighted average concentration ( $C_{\text{ppm-TWA}}$ ) during the entire re-

peated use exposure period (3.4 hours, corresponding to 205 minutes) according to the relationship:

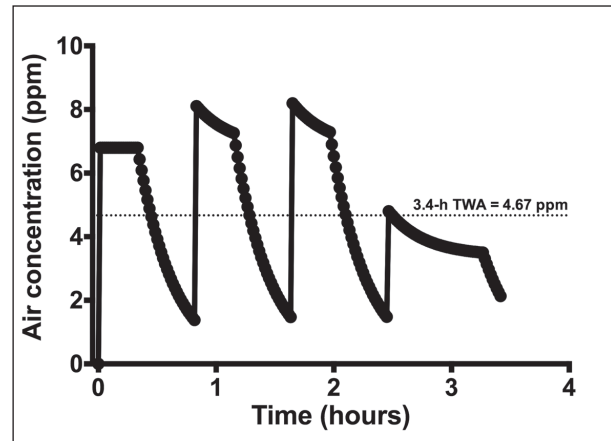
$$(5) \text{ Cppm} - \text{TWA} (3.4\text{h}) = \frac{C_{1\text{min}} + C_{2\text{min}} + C_{3\text{min}} + \dots + C_{205\text{min}}}{205 \text{ min}}$$

Peak ppm values were calculated as the maximum concentration after each topical sevoflurane application.

## RESULTS

Time of exposition and exposure results are summarized in table 1. As stated above, dosimeters were put in place after the treatment of the first patient, so that they were likely exposed to some residual sevoflurane. Both personal monitoring and stationary area sampling showed low to moderate degrees of ambient sevoflurane pollution during topical treatment of wounds. As expected, badges used for personal monitoring showed higher sevoflurane values. On the other hand, air pollution of the treatment room was lower with increasing distance from the stretch (dosimeters placed on walls had lower sevoflurane ppm-TWA values).

Peak concentrations of sevoflurane in air and overall TWA calculated via a conservative model (figure 2) were in excellent agreement with the values obtained by empirical occupational monitoring (table 1).



**Figure 2.** Modeled concentrations of sevoflurane in the air in the treatment room used for topical treatment. The usage rate of sevoflurane was close to 1 patient every 50 min, the volume of the room and the air changes used corresponded to the real scenario conditions (163 m<sup>3</sup> and 3.3 per hour, respectively). Each peak represents a new patient treated. The dotted line represents the ppm-TWA for the entire exposure period. The peak concentrations and the ppm-TWA remain under exposure limits set by occupational safety agencies from Finland, Sweden, and Norway.

Odor of sevoflurane in the room was evident at the end of the treatment of all patients, but neither headache nor any neurological disturbance (including sedation) were reported by patients, nurse, or physicians.

**Table 1** - Dosimeter monitoring conditions and environmental exposure

Dosimeter number and location <sup>a</sup>	Exposure time	Volume of sevoflurane used to treat patients (mL)	Environmental sevoflurane		
			Measured		Theoretical Peak concentrations calculated from simulations (ppm)
			Total sevoflurane in dosimeter (µg)	ppm-TWA <sup>b</sup>	
1-Nurse (patient 1)	20'	20	106.29	8.28	8.1
2-Nurse (patient 2)	20'	20	114.46	9.12	8.2
3-Nurse (patient 3)	50'	10	95.84	2.86	4.8
4-Nurse (all patients)	3 h 25'	50	856.93	8.48	4.67 <sup>c</sup>
5-Curtain	3 h	50	323.23	3.37	
6-Right Wall	3 h 20'	50	97.26	0.73	
7-Opposite Wall	3 h 20'	50	165.56	1.43	
8-Left Wall	3 h 20'	50	123.66	1.00	

<sup>a</sup> number of dosimeter (see figure 1). <sup>b</sup> ppm-TWA: parts per million - Time weighted average. <sup>c</sup> This peak value corresponds to 3.4 h-TWA.

## DISCUSSION

Occupational exposure of health-professionals to halogenated anesthetics inside and outside the operating room is a matter of concern (5,23), but evidence of adverse effects of anesthetic gases on health personnel is scarce and inconsistent (23). Focusing specifically on sevoflurane, confirmed seriously detrimental adverse health effects associated to occupational exposure have been scarcely reported so far, and they mostly consisted in immunological reactions affecting the skin or the airway (2, 6, 21, 32) although anecdotal report on neurological impairment has also been reported (7).

Irrigation of wounds with topical sevoflurane is an emerging pain treatment modality. A wide adoption of this new indication is expected to happen due to the rapid, intense and long-lasting analgesic properties of topical sevoflurane (12, 22), as well as its promising profile for reduction in healthcare costs. In fact, preliminary evidence has shown reduction in the number of visits to emergency departments due to pain (8), lesser hospital admissions as a result of adverse effects caused by systemic analgesics (opioids, NSAIDs) (8), and shorter hospital stay due to a potential antimicrobial effect (10). Thus, although the personnel working in the operating rooms are currently the most exposed to anesthetic gases, the number of health-care professionals occupationally exposed to sevoflurane would be greatly increased as topical sevoflurane becomes routine practice in the treatment of wounds. As a consequence, interest in studying all aspects of occupational exposure would be also increased.

Empirical and modelled data from this pilot study show that air concentrations of sevoflurane following topical administration to wounds were relatively low. Even under very conservative assumptions (instantaneous, complete evaporation with no absorption of sevoflurane by the patient, and uninterrupted presence of healthcare workers), and rather modest actual room air exchange (3.3 ACH), air concentrations of sevoflurane were always under exposure levels acceptable in European countries for anesthetic procedures. Levels measured in dosimeters placed at the nurse's breathing zone for short-term exposure (2.86, 8.28, and 9.12 ppm-TWA, table 1)

fell well below 20 ppm, which is the limit established in Finland and Sweden for short-exposure (17, 18). Levels measured in dosimeters placed in the room for long-term (0.73, 1.00, 1.43, and 3.37 ppm-TWA, table 1) fell well below 5 ppm, which is the lowest limit established in a European country, concretely Denmark (3). The level measured at the nurse's breathing area for long-term exposure (8.48 ppm-TWA) could be somewhat controversial because it was above the limit for Denmark, but at the same time it fell below the limits established in the other European countries, which range from 10 (17, 18, 23) to 20 ppm (1).

Concerning Spain, there is no established specific limit for sevoflurane occupational exposure (23). In Spain, the daily exposure limit for isoflurane—another halogenated anesthetic older than sevoflurane—is 50 ppm (13), which represents the average concentration at the breathing zone of the worker measured or calculated as a time-weighted average for an actual working day and in relation to a standard 8-hour working day. Taking into account that isoflurane is a more potent drug than sevoflurane both as an anesthetic and as to its potential for toxicity, safety exposure limits for sevoflurane should be higher than 50 ppm. However, the highest level measured at the nurse's breathing zone for long-term exposure (8.48 ppm-TWA) was far below this threshold of 50 ppm. Therefore, the exposition levels to sevoflurane obtained in this pilot study seems to fall into the safe range.

In line with this, none of the people implicated (patients, nurse, physicians) reported subjective symptoms during the study day. Patients included in the protocol for ambulatory topical sevoflurane consult on a monthly/bimonthly basis in a specific consult. Under these conditions the exposure of healthcare workers is brief and intermittent. This contrasts sharply with the prolonged and continuous exposure to anesthetic vapors in operating rooms. Thus, different occupational exposure limits could be necessary to protect healthcare workers using halogenated anesthetics in new clinical scenarios (11).

Healthcare workers in close proximity to the patients treated with topical sevoflurane may have been exposed (at least for a short period) to greater concentrations than those calculated with the

model or measured with the dosimeters. However, the conservative approach provides confidence that real-time peak values should have not been much different. In any case, it is impossible to document or simulate this exposure pattern due to the limitations of passive monitoring (19) or modelling assumptions (vapor concentration is an average for the entire procedure room volume). Further studies using infrared spectrometry equipment (14-16) would be suitable to establish a most accurate pattern of exposure through real-time vapor measurement. It is clear that having the infrared spectrometry equipment will make modelling unnecessary, but modelling will still be a useful alternative to estimate sevoflurane pollution in many hospitals lacking such equipment.

Although this pilot study was not conducted to specifically assess the risks related to sevoflurane exposition, the results obtained are very encouraging regarding the risk of exposure for healthcare workers adopting this new pain treatment option. Nevertheless, in order to decrease the current exposure to sevoflurane in air following topical application to wounds, the authors propose some recommendations and interventions to reduce occupational and environmental exposure to “the lowest practical level” (16) based both in the authors’ experience and in applying common sense. The first recommendation to all professionals eventually adopting this modality of treatment is to ask the institutional pharmacy services to prefill syringes with sevoflurane (9). Otherwise, charging the syringes immediately prior to drug application is recommended (20). Covering the wound with barrier dressings could be useful limiting sevoflurane evaporation and, once the desired effect is achieved, sevoflurane and contaminated materials could be quickly removed and disposed into sealable bags to contain any remnant. Another basic precaution consists in irrigating sevoflurane in well ventilated rooms (20), or with air renovation systems similar to those of operating theaters (29). Using the minimum effective dose of liquid sevoflurane will result in both environmental advantages, since sevoflurane causes greenhouse effect (28), and direct economical savings (which are modest in our setting, as every milliliter of sevoflurane costed approximately €0.30 in 2018).

In conclusion, irrigation of chronic wounds with liquid sevoflurane is becoming a new topical pain management alternative. Overall, this pilot study shows that air concentrations of sevoflurane following an approved protocol for topical administration to wounds seems to be safe since they fell into exposure limits accepted in multiple European countries for anesthetic procedures. In the absence of specific regulations for many countries, the lowest practical level may be attained by modifying some application conditions.

**Financial support:** Vapogenix Inc. financed the specific material (dosimeters) and shipping costs. This company had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

NO POTENTIAL CONFLICT OF INTEREST RELEVANT TO THIS ARTICLE WAS REPORTED BY THE AUTHORS

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Società Italiana  
Valori di Riferimento

**CONVEGNO:**  
**“I VALORI DI RIFERIMENTO PER LA MEDICINA  
 OCCUPAZIONALE E AMBIENTALE” DELLA SOCIETÀ  
 ITALIANA VALORI DI RIFERIMENTO (SIVR)**

**PAVIA, VENERDÌ 8 NOVEMBRE 2019**

Istituti Clinici Scientifici Maugeri  
 Centro Congressi - Via Maugeri, 6

**Programma**

8:30 Saluti delle autorità: Presidente SIVR, Presidente SIML, Presidente AIDII,  
 Direttore Scientifico centrale ICS Maugeri Spa SB-IRCCS

Ore 9:00-10:20 Moderatori: Pietro Apostoli, Marcello Imbriani

- **I valori di riferimento per la medicina occupazionale e ambientale: prospettive e sfide**  
*Ivo Iavicoli, Presidente SIVR, Professore Ordinario di Medicina del Lavoro,  
 Università degli Studi di Napoli Federico II*
- **L'importanza dei valori di riferimento nella epidemiologia occupazionale**  
*Enrico Oddone, Ricercatore TD di tipo B, Università degli Studi di Pavia*

Ore 10:20 -13:00 Moderatori: Anna Ronchi, Maurizio Bettinelli

- **La qualità del dato analitico nella definizione dei valori di riferimento**  
*Silvia Fustinoni, Professore Associato di Medicina del Lavoro, Università degli Studi di Milano*
- **I valori di riferimento per gli elementi metallici**  
*Piero Lovreglio, Segretario e Tesoriere SIVR, Ricercatore TD di tipo B,  
 Università degli Studi di Bari Aldo Moro*
- **I valori di riferimento per i composti organici volatili**  
*Fabiola Salamon, Dirigente Chimico, Università degli Studi di Padova*
- **I valori di riferimento per gli idrocarburi policiclici aromatici**  
*Anna Cenni, Dirigente Chimico, Laboratorio di Sanità Pubblica, Azienda USL Toscana sud est - Siena*

Ore 14:00-17:00 Moderatori: Ivo Iavicoli, Danilo Cottica, Stefano Massimo Candura

- **I valori di riferimento per i pesticidi**  
*Maria Cristina Aprea, Past President SIVR, Responsabile U.O. Tossicologia Occupazionale e Ambientale, Laboratorio  
 di Sanità Pubblica, Azienda USL Toscana sud est - Siena*
- **Valori di riferimento in ambito clinico-tossicologico**  
*Carlo Locatelli, Responsabile servizio CNIT, IRCCS Maugeri Pavia*
- **Il possibile contributo dei valori di riferimento all'igiene occupazionale**  
*Elena Grignani, Vicepresidente SIVR, Centro Ricerche Ambientali, ICS Maugeri Padova-Pavia -  
 Sara Negri, Consiglio Direttivo SIVR, Centro Ricerche Ambientali, ICS Maugeri Padova-Pavia*
- **La valutazione del rischio dei cancerogeni occupazionali e i valori di riferimento**  
*Enrico Pira, Professore Ordinario di Medicina del Lavoro, Università degli Studi di Torino*
- **I Valori di Riferimento tra speculazione, elaborazione ed applicazioni**  
*Pietro Apostoli, Professore Onorario di Medicina del Lavoro, Università degli Studi di Brescia*