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# Evaluating the relationship between cell viability and volatile organic compound production following DMSO treatment of cultured human cells

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*Received May 11, 2016, accepted July 12, 2016*

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*Pharmazie 71: 727–732 (2016)* *doi: 10.1691/ph.2016.6075*

Methylsulfinylmethane (dimethyl sulfoxide; DMSO) is widely used in clinical treatment and bioresearch. Moreover, there is bioconversion between methylsulfanylmethane (dimethyl sulfide; DMS), DMSO, and methylsulfonylmethane ($DMSO_2$) in mammalian metabolism. Due to the real-time detection limits for volatile compounds, most research has focused on $DMSO_2$ as a stable byproduct of DMSO. Therefore, details about the production of DMS as a byproduct of DMSO metabolism remain to be elucidated. Here, we report the characterization of trace-level volatile organic compounds (VOCs) produced following DMSO treatment of cultured human cells using an ultrasensitive vacuum ultraviolet photoionization mass spectrometer (VUV-PIMS). Using this approach, 24 h after DMSO treatment we detected 16.9 and 21 parts per billion by volume (ppbv) DMS in the atmosphere above the cells (headspace) within HeLa and 293T tissue culture flasks, respectively. When simultaneously exposed to 50 nM paclitaxel (PTX), 17.6 and 22.3 ppbv DMS were detected in the headspace of HeLa and 293T culture flasks, respectively. Nevertheless, at doses of PTX more or less than 50 nM, the detectable levels of DMS were reduced to as low as 8.4 ppbv. Our experimental results demonstrate that by co-administering 5 to 10 nM PTX with DMSO, it is possible to moderate the production of DMS considerably. However, at higher doses of PTX, increased apoptosis was observed that likely contributed to higher DMS production by cells.

## 1. Introduction

Methylsulfinylmethane (dimethyl sulfoxide; DMSO) is a water-miscible clear liquid, which is widely used not only as a cryopreservative for cells, but also as a transport medium to facilitate transcutaneous drug absorption (Yellowlees et al. 1980). In veterinary research, there has hardly been an animal species that has not been treated with DMSO (Muir 1996). Clinically, DMSO is extensively used as a topical analgesic and prescribed for a variety of ailments including pain, inflammation, interstitial cystitis, arthritis, skin disorders, and post-herpetic neuralgia (Higman et al. 2000). DMSO has been shown to delay cancer spread, prolong survival, protect non-cancer cells, and potentiate chemotherapeutic agents (Miller et al. 1990). DMSO was expected to be the Aspirin of our era; however, the principal side effect is an odd odor, which put off many drug companies and hindered its clinical application (Muir 1996). The unpleasant odor is a result of DMSO being reduced to methylsulfanylmethane (dimethyl sulfide; DMS) in mammalian tissues by methionine sulfoxide reductase A (MSRA) (Moskovitz et al. 1996). In most reported species, the DMS in the air exhaled over the 20 days following DMSO administration only accounts for approximately 3 % of the DMSO administered (Williams et al. 1966). Therefore, it is important to investigate ways of reducing the production of DMS while combining DMSO effectively with other drugs.

Apart from DMS, a number of volatile organic compounds (VOCs) are released by various normal metabolic and biochemical processes (Thorn and Greenman 2012; Fischer et al. 2015; Van der Schee et al. 2015), and the metabolism of these VOCs varies with cellular stresses (Haick et al. 2014). Therefore, the detection of VOCs emitted by cells can be used as a supplementary method to rapidly evaluate their metabolic status (Pasini et al. 2004; Mazzone 2008). Various techniques and instruments have been used to identify VOCs emitted by tissues and cells. Gas chromatography mass spectrometry (GC-MS), which is used as part of several pre-concentration techniques, remains the gold standard hybrid-analytical platform for uncovering new biomarkers from a diverse range of sources (Filipiak et al. 2008; Mochalski et al. 2013; Sponring et al. 2010). For example, the conversion of DMSO to DMS was discovered using GC-MS (Williams et al. 1966). However, GC-MS cannot be used to detect DMS in real-time and is not suitable for measuring other reactive VOCs. $^1$HNMR spectroscopy of body fluids has also been used to detect the products of DMSO metabolism, but owing to the limited number of assigned resonances, it can be only be used to detect bioconversion between DMSO and $DMSO_2$, not between DMSO and DMS (Engelke et al. 2005). Photoionization detection (PID) is a classical soft-ionization technique that has been used in the detection of VOCs (Muhlberger et al. 2001, 2002). We recently developed an ultrasensitive vacuum ultraviolet photoionization mass spectrometer (VUV-PIMS) with a parts-per-trillion (ppt) by volume (pptv) level of detail (LOD) (Sun et al. 2015). In this study, the VOC profiles of DMSO or DMSO and paclitaxel (PTX) treated HeLa and 293T cell lines were characterized in real-time using VUV-PIMS. Paclitaxel was added as a chemical to experimentally reduce cell viability, allowing us to study the relationship between cell viability and DMSO metabolism. The release of DMS was observed in all cases as expected. When co-treated with PTX and DMSO, the amount of DMS produced was dose related. Studying the link between VOCs, DMSO metabolism, and cell viability will provide important insights into how to adopt DMSO as a supplemental therapeutic technique while minimizing the side effect of unpleasant odor.

## 2. Investigations, results and discussion

### 2.1. *Evaluating the levels of DMS produced by cells following DMSO treatment*

Most of the volatile metabolites emitted from cells are present at low concentrations ranging from parts-per-billion (ppb) by volume (ppbv) to pptv; fortunately, the VUV-PIMS based system (Fig. 1)

used in this study allows real-time detection and quantification of pptv levels of VOCs without sample pre-concentration (Sun et al. 2015). To effectively evaluate the odor level resulting from DMS production in cells, the LOD of the instrument used should be superior to the human olfactory threshold of 400 pptv for DMS (Glindemann et al. 2006). The LOD of the VUV-PIMS for DMS was as low as 3.7 pptv in ambient air (Li et al. 2016), which surpasses the LOD of most MS-based techniques (Tsai et al. 2008). For example, the LOD of DMS in GC-MS is only 300 ppbv, and in proton transfer reaction MS (PTR-MS) the LOD of DMS is 50 pptv (King et al. 2010; Zheng et al. 2009). These methods are therefore not as sensitive as VUV-PIMS for evaluating subtle variations in DMS levels.

Figure 2 shows the VUV-photoionization mass spectra of VOCs from cells treated with 0.1 µL DMSO. As seen in Figs. 2a and 2b, both HeLa and 293T cells converted DMSO to DMS, yielding around 20 ppbv DMS in just 24 h. After 10 min of sampling, a steady gas-fluid exchange was achieved, and the signal intensities of DMS (*m/z* 62) stabilized at around 5000 counts (25 ppbv). In the 80 mL culture flasks, the addition of 0.1 µL DMSO could produce as much as 4500 parts per million by volume (ppmv) DMS (Fig. 2). Even so, due to the limited number of cells and the limited vaporization of the soluble DMS, only $5.5 \times 10^{-6}$ fraction of the available DMSO was detectable as DMS under the sampling pressure of $3.5 \times 10^{-3}$ Pa. DMS is a neutral compound that is stable in blood and can be transported from blood to air within the alveoli. On the other hand, it is also difficult to remove DMS from the bloodstream due to its neutral nature. To develop a proper DMSO therapy with an acceptable amount of odor, it is important to be able to quantify the levels of DMS produced following treatment with sensitivity comparable to that of the human olfactory system. Therefore, the technique described above is of clinical significance.

### 2.2. Changes in the VOCs produced by human cells following DMSO treatment

Based on the results shown in Fig. 2, there is no apparent distinction between the mass spectra produced by the VOCs from the HeLa versus 293T cell lines. Apart from *m/z* 62, another characteristic peak at *m/z* 104 was observed when DMSO was administered. This peak was assigned to styrene, which was likely to be a degradation product derived from the polystyrene flask. In principle, polystyrene resists acids, alkalis, and alcohol, but it can be broken down by some organic compounds (Kurbacher 1996). Since the signal intensity of styrene was significantly increased when DMSO was administered (Fig. 2), it is reasonable to assume that DMSO or a metabolic byproduct thereof cause the decomposition of polystyrene. Identifying the responsible chemical(s) will require further research.

Several other peaks were observed that were common to both DMSO treated and untreated cell cultures (Fig. 2). These peaks were assigned to compounds that have been reported previously in the analysis of the headspace of tissue culture flasks. The peaks at *m/z* 18, 19, 37, and 55 correspond to water, oxidanium ($H_3O^+$), $(H_2O)_2H^+$, and $(H_2O)_3H^+$. Spectral peaks at *m/z* 17, 28, 32, 45, 46 may be derived from azanes (ammonia) (Smith et al. 2003; Shin et al. 2009), molecular nitrogen (Brunner et al. 2011; Predieri and Rapparini 2007), molecular oxygen, acetaldehyde (Shin et al. 2009), and ethanol (Filipiak et al. 2008; Sponring et al. 2009), respectively. Propan-2-one (acetone) (Filipiak et al. 2010; Sponring et al. 2009) and propanal (Brunner et al. 2010; Sponring et al. 2009) could contribute to the peak at *m/z* 58. The peaks at *m/z* 43 and 63 are likely unidentified impurities in the cultured cells or the atmosphere. The intensities of the acetaldehyde peaks were 7682±159 and 5836±88 counts in the untreated HeLa and 293T cultures, respectively, and around 9000 counts in both the DMSO treated cultures (Fig. 2). It is believed that acetaldehyde in humans is produced mainly from hepatic ethanol metabolism by alcohol dehydrogenase (Wickramasinghe 1985, 1989), and alcohol dehydrogenase also shows a high tolerance to DMSO (Zhu et al. 2006). Based on the increased amount of acetaldehyde produced following DMSO administration, the alcohol dehydrogenase pathway might be stimulated by the presence of DMSO.

The signal intensity of the peak at *m/z* 58 increased from approximately 2500 counts to approximately 5000 counts when DMSO was added to both cell lines, however we cannot determine the relative contributions of propan-2-one and propanal to this increase (Fig. 2). There are two sources of propan-2-one production in cell metabolism: the decarboxylation of 3-oxobutanoate (acetoacetate) and the dehydrogenation of propan-2-ol (isopropanol) (Kalapos 2003). One or both of these reactions might be stimulated by DMSO. Propanal is believed to be a precursor of ethylene in metabolism (Lieberma and Kunishi 1967), and the intensity of the peak that corresponds to ethene (*m/z* 28) also increased significantly from approximately 1000 to 3000 counts when DMSO was

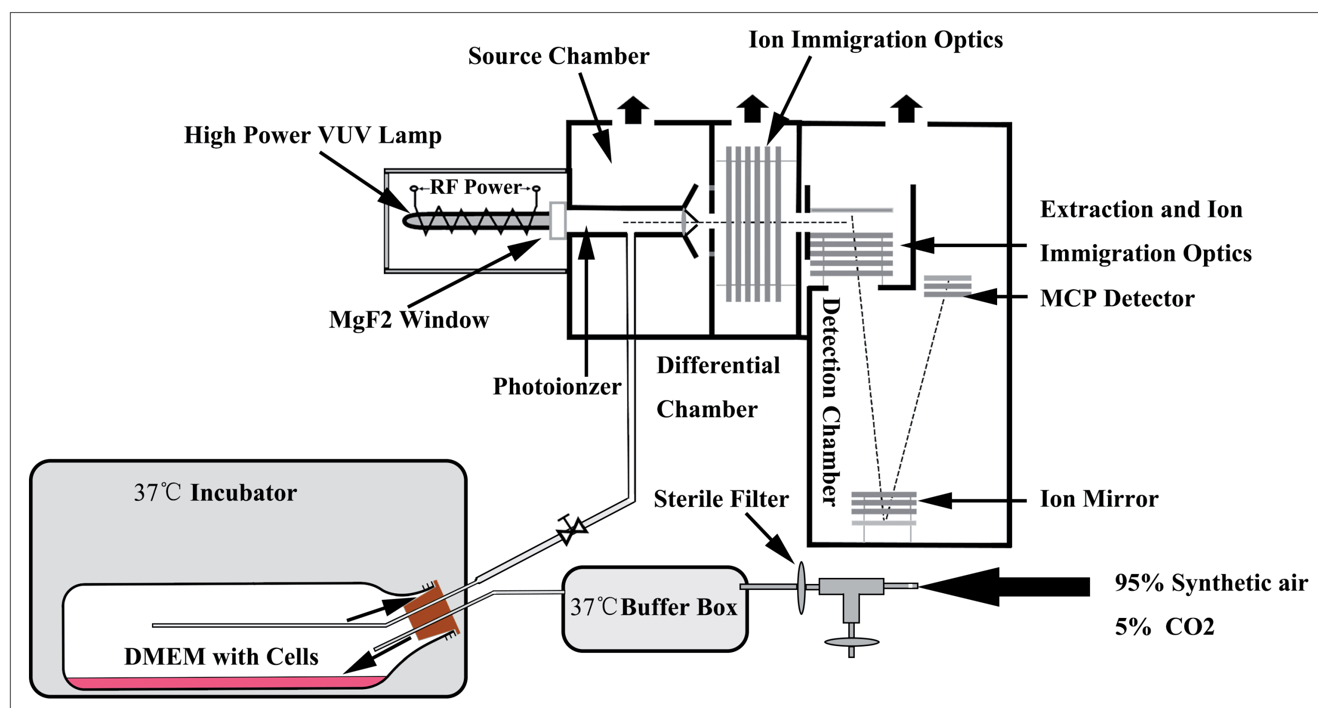


Fig. 1: The VUV-PIMS system for real-time VOC measurement in cultured cells. A schematic of the VUV-PIMS experimental setup is shown.

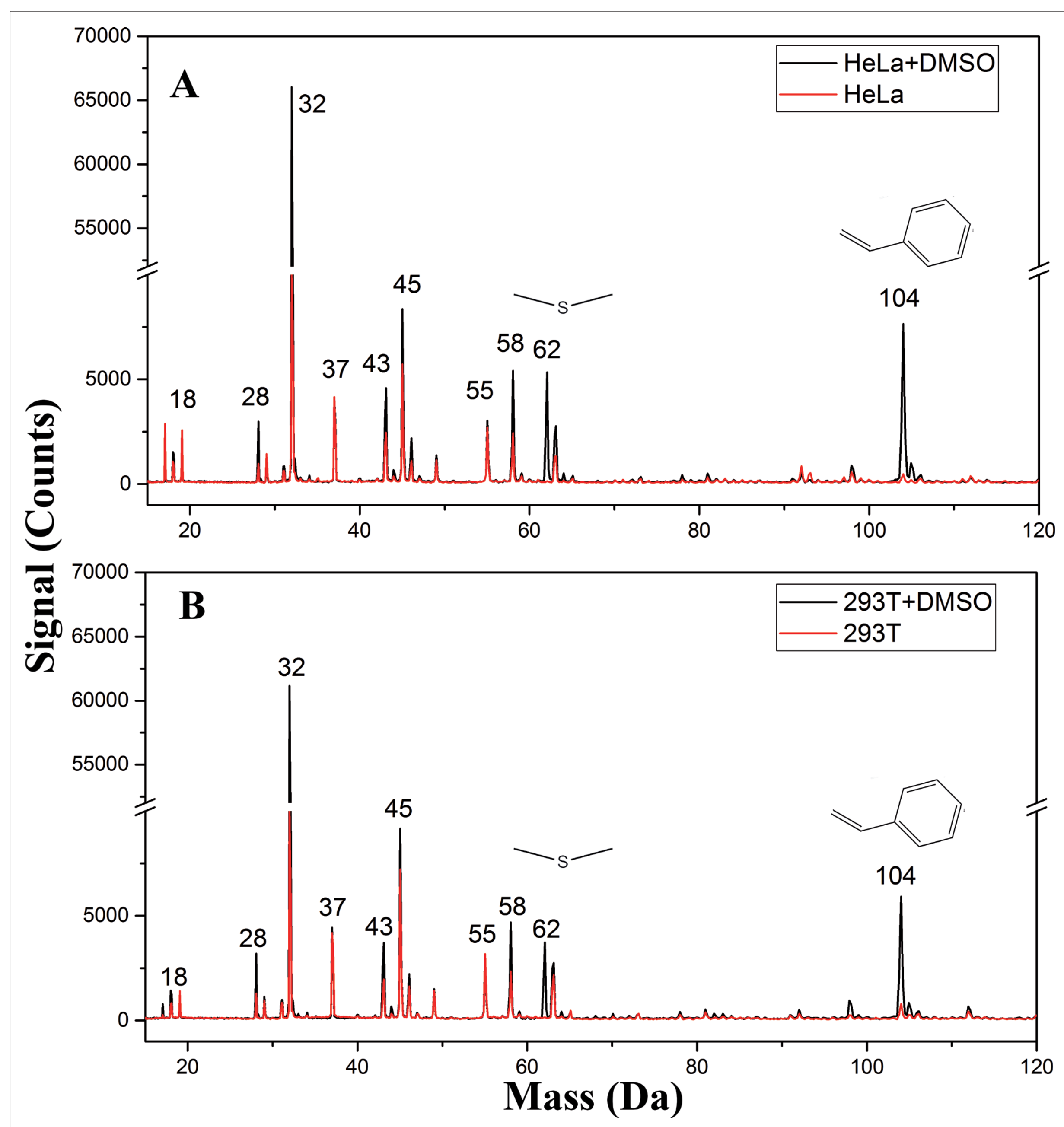


Fig. 2: A VUV-PIMS system was used to analyze airborne VOCs in the headspaces of tissue culture flasks, and the resulting mass spectra are shown. (A) The mass spectra of VOCs from flasks containing HeLa cultures with or without the addition of 0.1 µL DMSO are shown. (B) The mass spectra of VOCs from flasks containing 293T cultures with or without the addition of 0.1 µL DMSO are shown.

present. This observation would be consistent with an increase in propanal production following the addition of DMSO to the media. In summary, the levels of several VOCs detected in the headspaces of cell culture flasks containing HeLa and 293T were found to be increased following DMSO treatment. Our VUV-PIMS instrument has therefore allowed us to shed light on the relationship between an administered drug and metabolic pathways involving VOCs. Details about the mechanisms of acetaldehyde, propan-2-one, propanal, and ethene production under DMSO stress remain to be elucidated in further pharmacological experiments.

### *2.3 Impact of cell viability on the production of DMS following DMSO treatment*

To evaluate the extent to which DMS is produced and how DMS production changes with cell viability, a series of concentrations of PTX (0 nM, 5 nM, 10 nM, 50 nM, and 100 nM) dissolved in 0.1 µL DMSO were added to cell cultures. The DMSO added in this experiment made up substantially less than 0.5 % of the total volume of tissue culture media, and thus should not have affected cell growth or viability (Murakami et al. 2002). As shown in Fig. 3, there was a reduction in the amount of DMS produced when low doses of PTX (5 and 10 nM) were added, and there was a subsequent increase in the amount of DMS produced when a 50 nM PTX solution was added. The detected levels of DMS from HeLa cultures treated with 50 nm PTX reached 4399±134 counts, representing a partial restoration to the levels produced by the untreated HeLa cultures (5252±74 counts). The levels of DMS detected from the 293T cultures reached 5633±46 counts when 50 nM PTX was added, exceeding the levels of DMS from the untreated 293T cultures (4348±113 counts). Conversely, when a 100 nM PTX solution was added the amount of DMS produced was decreased in both cell lines, although in the case of the 293T cultures the amount still exceeded the amount produced when no PTX was added. When treated with 10 nM PTX, the DMS signal

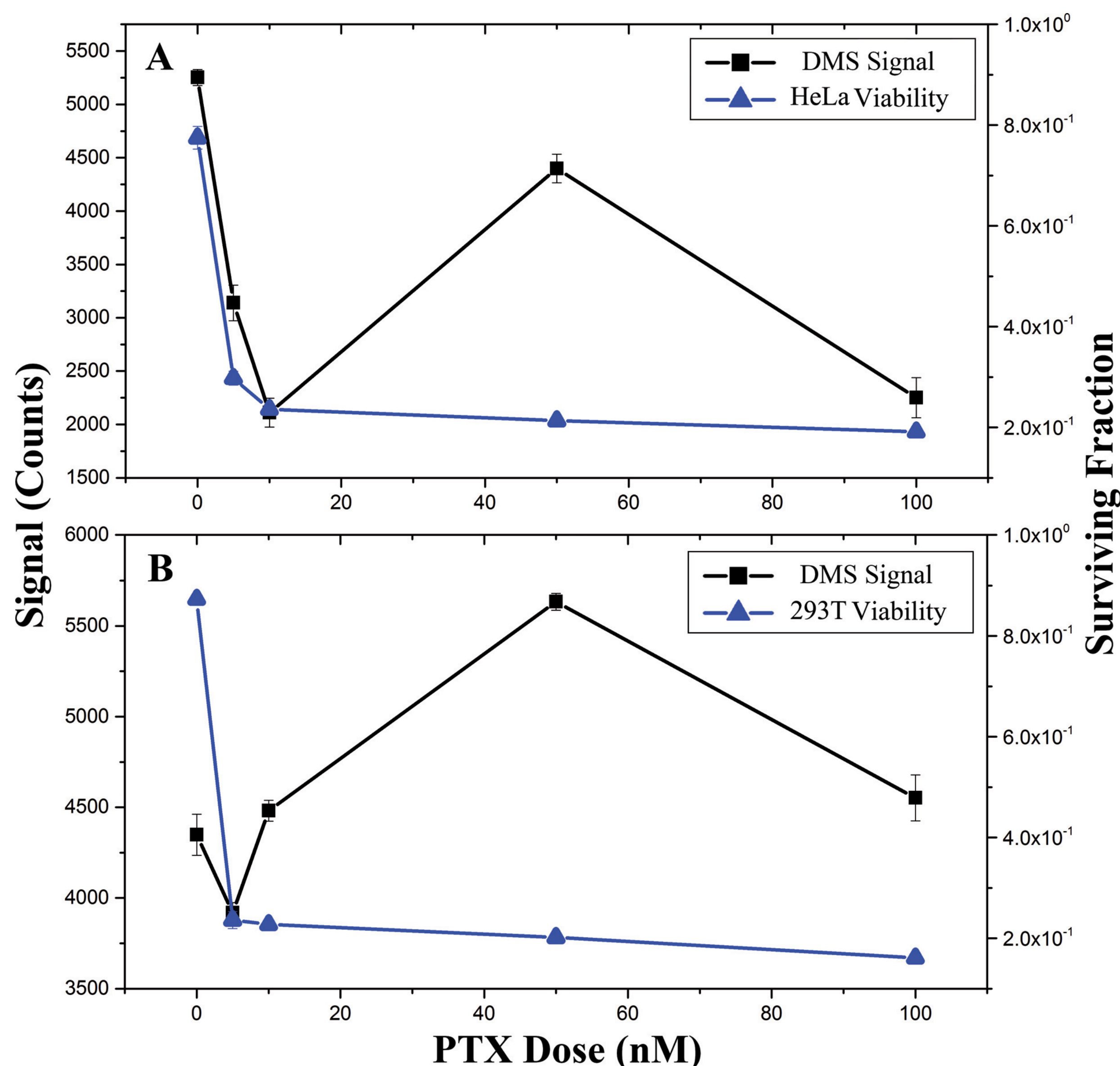


Fig. 3: The production of DMS as determined by VUV-PIMS (left vertical axis) and the viability of cells as determined by CCK8 assay (right vertical axis) are shown following treatment of HeLa (A) and 293T (B) cultures with various concentrations of PTX.
Results are the average of three replicates, and error bars represent one standard deviation

intensities from the HeLa cell cultures decreased from 5252±74 to 2110±135 counts. The DMS signal intensities from the 293T cultures were reduced from 4348±113 to 3918±56 counts when 5 nM PTX was administered.

The viability of cells decreased in a dose-dependent manner upon addition of PTX (Fig. 3), and similar declines in cell viability were observed for both cell lines with increasing PTX doses. We next used phase-contrast microscopy to evaluate the morphology of cells under each condition. Figure 4 shows micrographs of HeLa cells under various treatment conditions, and Figure 5 shows micrographs of 293T cells under various treatment conditions. Treatment with lower levels of PTX (5 nM or 10 nM) or DMSO alone only slightly affected the morphology and density of the cultured cells. On the contrary, treatment with 50 or 100 nM PTX affected the condition of the cells appreciably; widespread rounding-up of cells was observed, suggesting that apoptosis was extensively induced in 293T and HeLa cultures. Notably, 293T and HeLa cells under the stress of 50 nM PTX produced the most DMS (Fig. 3), this might be a result of apoptosis and the accompanying increase in methionine degradation byproducts, which include DMS (Kaji et al. 1981). Overall, the combination of DMSO with 5 to 10 nM of PTX can reduce the resulting DMS odor dramatically, without causing widespread destruction of the cells.

Given the multiple potential clinical uses of DMSO that are hindered by the side effect of DMS-odor, discovering a way to reduce the metabolic production of DMS following DMSO treatment is a very important goal. The findings and approach reported here may be informative for the future design of better DMSO-based therapeutics that not only moderate this side effect but also have increased potency.

## 3. Experimental

### *3.1. Cell cultures and measurements*

Two human cell lines were employed in the study: cervical cancer cells (HeLa), and human embryonic kidney cells (293T). These cell lines were stored at the State Key Laboratory of Environmental Chemistry and Ecotoxicology at the Research Center for Eco-Environmental Sciences (Beijing, China). Cells were cultured in Dulbecco's Modified Eagle Medium (DMEM) (Gibco, Life Technologies, Gaithersburg MD) supplemented with 10 % fetal bovine serum (Hyclone, South Logan, UT), and 1 % penicillin/streptomycin (Corning, NY, USA). Cell lines were cultured in 25 $cm^2$ flasks in 10 mL of culture media for a minimum of 48 h. Cells were seeded at densities of 80–100 × $10^4$ cells/mL (> 90 % confluency) such that cell proliferation had plateaued before introduction into the VUV-PIMS measurement system or exposure to PTX. Three replicates were performed for each experimental group, and a media-only

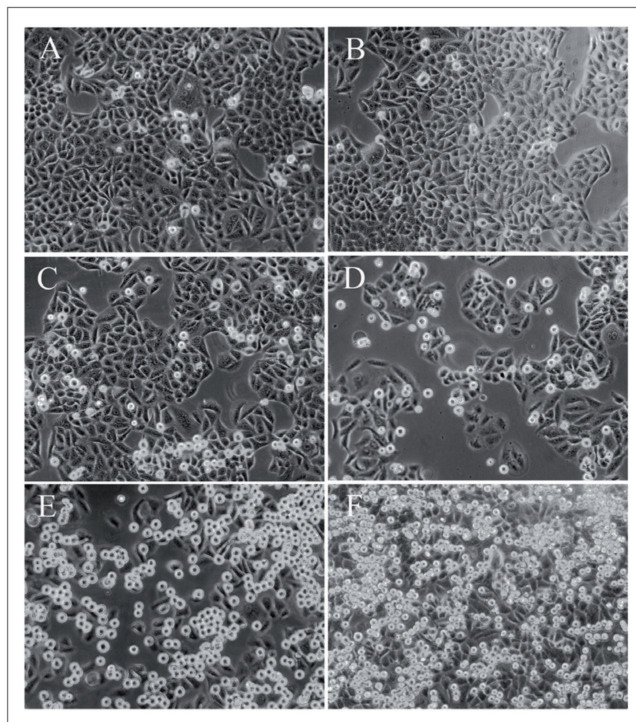


Fig. 4: Phase-contrast microscopy images of untreated HeLa cells (A), HeLa cells treated with DMSO only (B), and HeLa cells treated with 5 nM PTX (C), 10 nM PTX (D), 50 nM PTX (E) and 100 nM PTX (F) are shown.

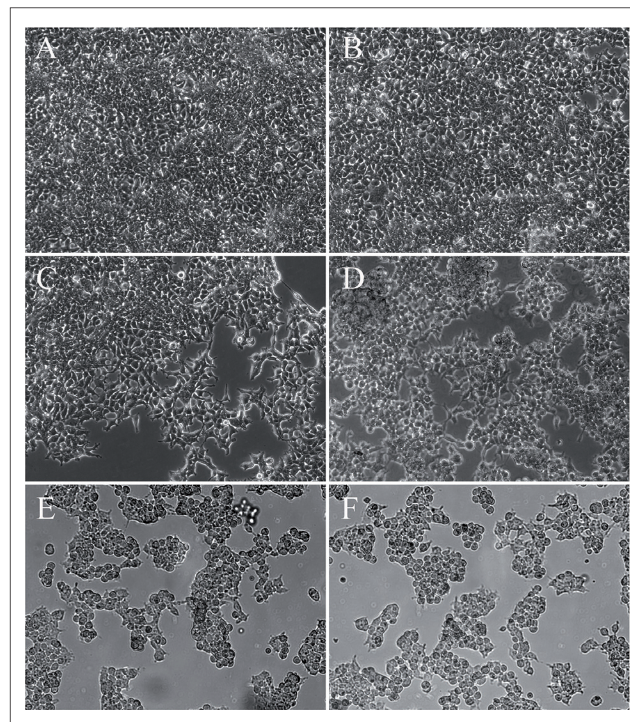


Fig. 5: Phase-contrast microscopy images of untreated 293T cells (A), 293T cells treated with DMSO only (B), and 293T cells treated with 5 nM PTX (C), 10 nM PTX (D), 50 nM PTX (E) and 100 nM PTX (F) are shown.

(no DMSO or PTX added) control was included. For the PTX-treated cell lines, 0.1 µL solutions of PTX at concentrations of 0, 5, 10, 50, and 100 nM in DMSO were added and cultures were subsequently incubated for 24 h (Liebmann et al. 1993; Kurbacher 1996). For all experiments, cell lines were cultured at 37 °C in a humidified atmosphere containing 5 % $CO_2$. Phase-contrast microscopy images of cells were taken using an inverted phase-contrast fluorescence microscope (Zeiss Axiovert 200, Germany). Cell viability was assayed using a CCK8 assay, wherein 10 µL of CCK-8 solution (Dojindo Molecular Technologies, Inc.) was added to each well, and the 96-well plate was incubated at 37 °C for 1 h. The optical density (OD) at 450 nm of each well was then measured on a microplate reader to determine the cell viability (Multiskan Microplate Photometer, Thermo, USA).

### 3.2. Measurement of VOCs in tissue culture flask headspaces

As illustrated in Fig. 1, mass-spectrometry based analyses of the VOCs in the headspaces of flasks containing either a cancer cell line (HeLa) or a non-cancer cell line (293T) were conducted. The measurement system mainly comprised a VUV-PIMS, an incubator, a sterile buffer box, and filters. Cells were incubated in 25 $cm^2$ culture flasks (80 mL), which were closed with a Teflon plug. Two holes were punched in each Teflon plug to allow a pair of 3.1755 mm (outer diameter) steel tubes to be passed through. To ensure proper mixing of the air in the flask headspace, the tube connected to the VUV-PIMS sampling tube protruded 3 to 5 cm deeper than the other one, which served as an inlet for the synthetic air (80 % $N_2$, 20 % $O_2$) and $CO_2$ stream. A sterile buffer box maintained at 37 °C was installed between the sterile filter and the inlet tube, to avoid any dramatic fluctuations in the gas being added to the culture flask. The buffer box was equilibrated with the synthetic air and $CO_2$ stream for several minutes before any measurements were performed. The synthetic air flux and $CO_2$ flux were set at 0.2 L/min and 0.01 L/min, respectively.

The VUV-PIMS system was recently developed in our laboratory and has been previously described elsewhere (Sun et al. 2015). Briefly, it comprises a vacuum ultraviolet (VUV) photoionization source, a sample inlet, and a short V-shaped time-of-flight mass spectrometer (TOF-MS). The VUV photoionization source is based on a krypton lamp outputting a photon flux of approximately $5 \times 10^{14}$ photon/s at a wavelength of 123.9 nm (Shu et al. 2013). The ambient sample inlet consists of a stainless steel tube (3.1755 mm outer diameter) and a precision needle valve. The sample flow is maintained at approximately 1 $cm^3$/s without pre-concentration. The TOF-MS is equipped with a free flight distance of 460 mm, chevron microchannel plates, a 100 × amplifier (Ortec VT120C), and a TOF multiscaler (FAST Comtec, P7888). The pressure of the detection chamber is maintained at around $3.5 \times 10^{-3}$ Pa. To evaluate the levels of DMS precisely, the data collected after 10 min of sampling were used, as by this time a stable gas-fluid exchange had been achieved (Li et al. 2016).

### 3.3. Reagents and gases

The volume of 0.1 µL of DMSO (Sigma Chemical Co., MO) was adopted as the optimal volume for both the investigation of DMS conversion by cell lines and the dissolution of drug. To evaluate the relationship between DMSO metabolism and cell viability, PTX (99 % purity; BBI, Shanghai, China) was added to cell cultures at over 90 % confluency. Owing to its poor solubility in water, PTX was dissolved in DMSO (Liebmann et al. 1993). Cell viability was evaluated by CCK-8 assay (Dojindo Molecular Technologies, Inc.). High-purity (> 99.999 % pure) synthetic air, nitrogen, and $CO_2$ were purchased from Beijing Haikeyuanchang Practical Gas Co. Ltd. and Beijing Huayuan Gas Chemical Industry Co. Ltd., respectively.

Acknowledgments: This study was supported by the Strategic Priority Research Program of the Chinese Academy of Sciences (XDB05040501) and Creative Research Groups of China (Grant No. 51221892).

Conflicts of interest: None declared.

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