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Potential biomarkers of skin cancer diagnosis revealed through volatile metabolomics – A prospective research study

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ABSTRACT

Introduction: Skin cancer sites are known to release volatile organic compounds (VOCs) and these compounds can be collected and analysed to aid in the chemical profiling of skin cancers.
Patients and methods: We designed a new solid phase micro extraction (SPME) adaptation which allows portable collection of skin VOCs using a combination of direct contact and headspace collection modes. VOC samples were collected from 20 clinically diagnosed skin cancers, a non-affected area of each patient as a control, and samples from a volunteer group as a separate control.
Results: Our new device adaptation of polydimethylsiloxane (PDMS) / divinylbenzene (DVB) SPME was found to retain a variety of VOCs, and showed superior VOC collecting performance compared to other techniques. GCMS analysis revealed specific VOCs present in skin cancers not demonstrated in non-affected areas on healthy volunteers.
Conclusion: Hexadecanoic acid was the most frequently discovered compound in the skin cancer group. Our new approach to SPME collection of VOCs shows promise for future study of VOC skin cancer biomarkers.

1. Introduction

The incidence of skin cancers is increasing in Europe, North America, and Australasia [1]. In Dorset, UK, recent years have seen over a 30 % rise in skin cancer presentations [2]. Early detection and defined treatment plans are critical for most skin cancers, and recent immunotherapy successes for malignant melanoma highlight the importance of early diagnosis. Diagnostic tools include clinical examination by trained clinicians, dermatoscopes, and in specialist centres, confocal microscopy. Often, patients self-examine for persistent lesions, present to primary care, and diagnosis is confirmed histologically. Most non-melanoma skin cancers can be treated with minimally invasive modalities if recognized early.

Biochemical research using mass spectrometry (MS) and nuclear magnetic resonance (NMR) emphasizes metabolic fingerprinting to identify chemical patterns aiding diagnosis [3–5]. In particular, volatile organic compounds (VOCs) serve as non-invasive biomarkers to differentiate cancerous from normal cells [6–8]. This relies on physiological processes releasing VOCs as by-products [9,10]. Thus, pathophysiological changes can be assessed by analyzing body matrices for qualitative and/or quantitative VOC shifts [11,12]. VOC detection as biomarkers is more developed in cancers like colorectal [13,14], breast [15,16], and lung [17,18]. However, VOCs can also be extracted from melanoma tissues [19–21]. Gas Chromatography-Mass Spectrometry (GC-MS) is favoured for detecting a broad range of VOCs in complex matrices [22,23], with sensitivity in the ppm–ppt range [24], and the ability to separate analytes for identification [25,26].

Solid-phase micro-extraction (SPME) is an effective technique to capture low-concentration disease-related metabolites [25,27]. SPME is rapid, easy to operate, and portable [28,29]. It does not require organic solvents, as the fibre can be directly injected into the GC for analysis [27, 30]. Most volatolomic studies recommend head-space SPME (HS-SPME) [25,31], enabling efficient collection and concentration of VOCs [32]. Gallagher et al. [33] identified 90 VOCs emitted from forearm and upper back skin using HS-SPME and GC-MS, employing small funnels to create closed environments. Significant differences were found by site (e.g., hexyl salicylate more common on backs, dimethylsulphone on forearms) and age (nonanal and benzothiazole more prominent in older subjects).

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Dormot et al. [34] demonstrated that gentle stroking of the SPME fibre on skin (direct contact, DI-SPME) for 3 min yielded similar VOC profiles to 45 min HS-SPME, detecting compounds like nonanal, octanal, decanal, and methylheptenone from human foot skin. DI-SPME proved effective both in lab and field settings. Jiang et al. [35] introduced a thin-film SPME (TF-SPME) [36] method to sample skin VOCs after cosmetic application (e.g., isopropyl palmitate, toluene, dodecanal). This involved sandwiching a PDMS membrane between stainless steel mesh, covered with aluminium foil to prevent direct skin contact. This minimized contamination from skin lipids and dust, maximizing human skin VOC collection and reducing GC-MS contamination.

Here we present a new technique, direct contact / headspace solid phase microextraction (DC/HS– SPME), for measuring VOCs to assess biomarkers for diagnosing skin cancer. Our adaptation of the SPME application was trialled on a cohort of skin cancer patients and a volunteer group. Our technique development and trial results are described here.

2. Methodology

2.1. Equipment and instrumentation

For SPME experiments we used a modified SPME portable field sampler from Supelco, with a 65um PDMS/DVB fibre. SPME fibres were conditioned before use following manufacturer instructions, and we ensured a blank fibre response before each patient or volunteer sample by injecting a fibre blank on the GCMS. VOC analysis took place on an Agilent Technologies 7890B GCMS, with MassHunter software.

Following method optimisation for both the SPME and GCMS approach, we used the following analytical method for all patient and volunteer skin VOC analysis:

GCMS was set to manual splitless injection with purge to split vent at 2 min (50 ml/min). Inlet temperature was 250°C, with helium as the carrier gas, and pressure at 9.2 psi. We used an Agilent HP-4ms ultra inert GC column (30 m x 250um x 0.25um), with the following temperature programme: initial temperate 40°C hold time of 2 min, followed by a ramp increase of 6 °C/min until 260°C which was held for 5 min for a total run time of 43.6 min. Transfer line was set to 250°C. The MS was operated in full scan mode, electron impact, with source temperate at 230°C, electron energy at 70 eV, starting mass set to 45 *m/z*, end mass at 350 *m/z*, scan time 200 ms.

VOCs were identified using NIST 20, considered the gold standard for mass spectral libraries. To ensure confidence in compound identity we set a threshold for reporting at 90 %. The high threshold of 90 % reduces the occurrence of false positive identifications significantly.

2.2. Method optimisation for SPME

To optimise SPME for skin VOC collection, several experiments were conducted to identify the method yielding the widest VOC range and greatest abundance. All tests used the forearm of one healthy volunteer (no cancer), with skin pre-cleaned using water. Each experiment was run in triplicate. Room air samples (30 min) were collected alongside each test to identify potential environmental contaminants.

1. **SPME above skin:** Fibre placed 1 cm from skin with sampling times of 10, 20, and 30 min.
2. **Direct contact SPME:** Fibre lightly wiped across ~1 cm^2 of forearm skin for 1, 2, 3, 4, and 5 min.
3. **SPME within bag:** Fibre placed 1 cm from skin, forearm enclosed in polythene forensic bag; sampling at 10, 20, and 30 min.
4. **Combination of direct contact SPME and bag:** Fibre wiped across ~1 cm^2 skin for 1–5 min, then placed 1 cm from skin inside bag for 10, 20, and 30 min.

After these, optimum direct contact sampling times were determined and applied in further tests:

1. **SPME in glass funnel enclosure:** Fibre housed in a 5 cm diameter funnel sealed lightly on skin, exposed 1 cm above skin; sampled for 10, 20, and 30 min.
2. **Combination of direct contact SPME and glass funnel:** Fibre wiped over ~1 cm^2 skin for 3 min, then placed in funnel as above for 10, 20, and 30 min.
3. **SPME in modified headspace vial:** Fibre housed in inverted 10 ml headspace vial with 3 mm hole at base; vial placed open-end on skin, headspace sampled for 10, 20, and 30 min.
4. **Combination of direct contact SPME and modified vial (DC/HS-SPME):** Fibre wiped over ~1 cm^2 skin for 3 min, then housed in inverted 10 ml vial as above; headspace sampled for 10, 20, and 30 min. This approach is shown in Fig. 1.

2.3. Participants

Participants (n = 30) included healthy people aged 18 + , (n = 10, non-skin cancer) and patients (n = 20) with skin cancer aged 18 + .

2.4. Recruitment

Patients with confirmed skin cancer were identified by a cancer specialist at participating hospitals. Eligible participants were over 18, English-speaking, and had skin cancer located on the head. Healthy volunteers (n = 10) were recruited from Bournemouth University staff and students.

Inclusion criteria – Patients:

- Diagnosed or suspected skin cancer, attending clinics
- Aged 18 or older
- English-speaking and literate
- Able to provide informed consent
- Accessible sample sites: arms, shoulders, chest, legs, back, stomach, abdomen

Inclusion criteria – Healthy volunteers:

- Aged 18 or older
- English-speaking and literate
- Able to provide informed consent
- Accessible sample sites as above

Exclusion criteria (both groups):

- History of strong allergies
- Under 18 or lacking capacity to consent
- Non-English speakers without an interpreter
- Unable to provide written informed consent

2.5. Methodology for patient trial

Following the method optimisation experiments described above the optimum SPME procedure was chosen (experiment 8, Fig. 1) and applied during VOC sampling from patients and volunteers in our study. The methodology was as follows:

Skin cancer patients (n = 20) each donated 2 skin VOC samples during a routine appointment: one from skin cancer lesion, one from skin not affected by skin cancer lesion. SPME samples were collected sequentially, at the same appointment. The skin area was cleaned with water prior to sampling, and a SPME sample of room air was collected (30 min sampling) for comparison with skin VOCs. The SPME fibre was gently wiped across the skin cancer lesion for 3 min and then held statically 1 cm above the lesion for 30 min enclosed in the modified 10 ml headspace vial. Here the air above the skin is enclosed, allowing

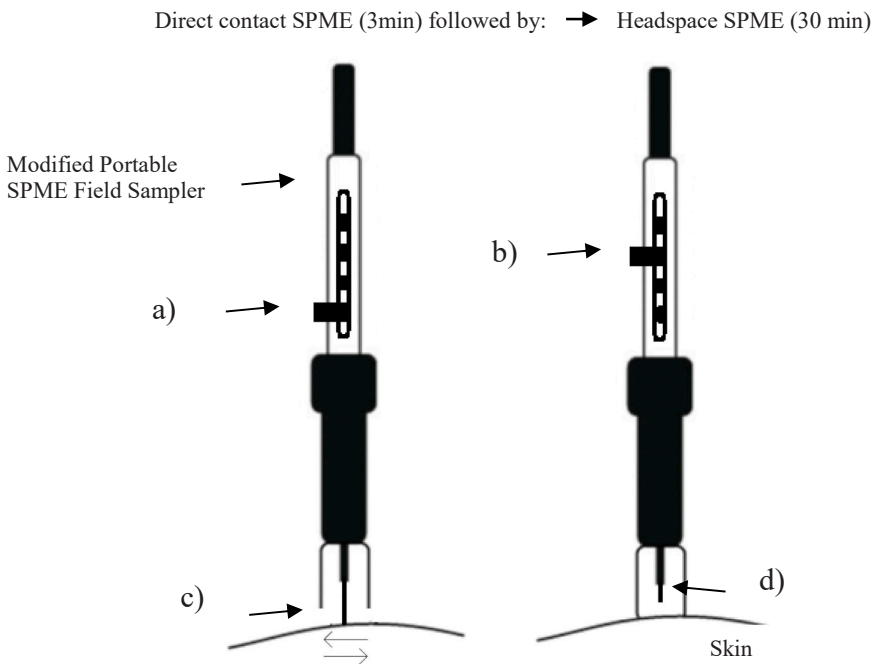

Fig. 1. Our modified SPME approach for VOC collection from skin cancer sites. a) portable field sampler set to position 4 extends the SPME fibre beyond the glass enclosure to enable direct skin contact, b) in position 2 the SPME fibre is held 1 cm above skin, and remain within the glass enclosure enabling headspace collection, c) shows direct fibre contact to skin, d) position of fibre when sampling in headspace mode.

VOCs to build up, providing optimum conditions for sampling. In addition to sampling VOCs from the skin cancer lesion each patient also provided a skin VOC sample from skin not affected by skin cancer. This serves as a control sample for comparison purposes.

After sampling with the DC/HS-SPME device the SPME fibre is retracted into the body of the device which is sealed behind a septum. The SPME devices are then transported to the laboratory for analysis, directly following the completion of the sampling.

2.6. Ethics

Ethical permission for this study was granted by NHS Health Research Authority – London Hampstead Research Ethics Committee, reference ID 20/LO/0899.

3. Results

3.1. Optimisation of the SPME technique for skin cancer VOC sampling

Method optimisation showed that experiment 8 (DC/HS-SPME) provided the best results, combining high VOC yield with portability and ease of use. Minimal VOCs were captured without an enclosure. Testing a bag, funnel, and modified vial showed VOC abundance increased as headspace volume decreased (vial < funnel < bag). Bags and funnels proved impractical clinically. Our modified 10 ml vial used in DC/HS configuration (Fig. 1) was both effective and convenient. Combining 3 min of direct contact with 30 min of headspace SPME maximised recovery of volatile and heavier skin compounds.

3.2. Participant data

The volunteer group (n = 10) was 50 % female, with mean age of 23 years. Volunteers were all white British, with one volunteer identifying as mixed race – white, and black Caribbean. Cancer patient group (n = 20) were 90 % male, mean age of 78.6 years, and all identified as white British. Cancer type within the group was 12 SCC, 7 BCC, and 1 patient with melanoma. All patients had skin cancer present on their face or head.

3.3. VOC identification

The number of VOCs identified in individual skin cancer patients ranged from 42 to 120. Since VOCs were sampled from two locations per patient, the cancer site and a separate non-cancerous skin area as a control, this enabled comparison to identify compounds potentially associated with cancer. Any VOCs also found in the general population control group (people without skin cancer) were excluded. The most frequently detected compound across all patients was hexadecanoic acid (palmitic acid), observed in 9 of 20 patients (5 with SCC, 4 with BCC). Hexadecanoic acid was also found at control sites in 3 patients (patients 1, 3 and 6). Patients 1 and 6 showed hexadecanoic acid in both cancer and control sites, whereas in patient 3 it was present only at the control site. Table 1 lists VOCs found exclusively at skin cancer sites. For comparison, Table 2 lists VOCs detected only in control areas of skin cancer patients. These compounds were absent from both the cancer sites and the general population control group.

4. Discussion

The results of this study indicate that combining direct contact and headspace SPME (DC/HS-SPME) is an effective, non-invasive method for sampling skin cancer-related VOCs. VOC profiles generated by our DC/HS-SPME GCMS approach revealed distinct VOCs from skin that may serve as cancer biomarkers. While volatile metabolomic signatures have been more extensively explored in colorectal [37,38,7], lung [39,40], and breast cancer [41,15], Abaffy et al. identified dodecane, undecane, and 4-methyl decane as prominent VOCs in melanoma biopsies [42]. Building on this, we identified VOCs potentially indicative of basal cell carcinoma, squamous cell carcinoma, and melanoma.

Generally, candidate cancer biomarkers fall into five VOC groups: aldehydes, ketones, alcohols, hydrocarbons, and aromatic compounds. Janfaza et al. highlighted eicosanals (1-Eicosanol, cis-13-Eicosenoic acid, Eicosyl benzoate), the epoxide Oxirane, tetradecyl-, and cis-10-Heptadecenoic acid as potentially cancer-specific [9]. Our results

Table 1
VOCs present *only* from skin cancer sites.

Patient	Molecular Identity	Retention time (min)	SCC	BCC
4 (SCC)	1,2-Pentanediol	7.66	✓	
2 (SCC)	17-Pentatriacontene	34.29	✓	
15 (SCC)	1-Octadecanesulfonyl chloride	11.84	✓	
16 (SCC)	1-Octadecyne	13.25	✓	
5 (BCC)	2-Methoxy−4-methyl−1-pentylbenzene	22.24		✓
6 (BCC)	9-Hexadecenoic acid, eicosyl ester, (*Z*)-	40.61		✓
17 (SCC)	Acetoin	3.02	✓	
1 (SCC)	α-Isomethyl ionone	20.54	✓	
13(SCC)	Benzaldehyde	8.71	✓	
2 (SCC)	Benzene, 4-ethyl−1,2-dimethyl-	10.76	✓	
3 (SCC)	Benzene, 1,2,4,5-tetramethyl-	11.45	✓	
13(SCC)	Benzene, 1-methyl−3-(1-methylethyl)-	12.55	✓	
1 (SCC)	Benzene, 2,4-diisocyanato−1-methyl-	17.81	✓	
18 (BCC)	(*Z*)−10-Heptadecenoic acid	30.56		✓
6 (BCC)	(*Z*)−10-Heptadecenoic acid	30.56		✓
6 (BCC)	2-Hydroxycyclopentadecanone	27.32		✓
4 (SCC)	(1*E*,3*E*,12*Z*)−1,3,12-Nonadecatriene−5,14-diol	27.25	✓	
6 (BCC)	(*E*)−9-Tetradecenoic acid	25.58		✓
4 (SCC)	1-(2,3,4,7,8,8a-Hexahydro−3,6,8,8-tetramethyl-1H−3a,7-methanoazulen−5-yl)ethanone	26.17	✓	
6 (BCC)	2-[4,5-Dihydro−5-(4-methoxyphenyl)−3-(4-methylphenyl)−5-isoxazolyl]−1-phenylethanone	12.34		✓
14 (BCC)	Hexanoic acid, 3,5,5-trimethyl-, 2-ethylhexyl ester	24.6		✓
3 (SCC)	Indolizine	16.51	✓	
17 (SCC)	Levomenthol	14.23	✓	
1 (SCC)	Linalyl acetate	15.60	✓	
1 (SCC)	2-Methoxynaphthalene	19.89	✓	
17 (SCC)	Dimethyldiethoxysilane	8.73	✓	
6 (BCC)	Terpinen−4-ol	13.79		✓
4 (SCC)	2,6,10-Trimethyltetradecane	18.85	✓	
4 (SCC)	α-Bisabolol	24.55	✓	

support these, showing elevated levels in cancer patients of palmitic acid (hexadecanoic acid), its metabolite hexanoic acid, methyled benzenes, phthalic acid, and dodecane. Although cis-10-heptadecenoic acid was found in basal cell carcinoma samples, it is more likely derived from E. coli on the skin and not cancer-specific [43].

Eicosanols, metabolites of polyunsaturated fat degradation via cyclooxygenases, lipoxygenases, cytochrome P450, or nonenzymatic pathways in inflammatory cells [44], were detected only in cancer patients. These included 1-eicosanol, cis-13-eicosenoic acid, and eicosyl benzoate—possibly all metabolic products of 1-eicosanol. This aligns with previous findings identifying 1-eicosanol as specific to melanoma [45].

Palmitic acid (hexadecanoic acid) has previously been proposed as a cancer biomarker. A 2012 melanoma study showed a 35-fold increase in its precursor, 1-Hexadecanol, compared to control skin [45]. This may reflect cancer-related upregulation of fatty acid synthesis for membrane formation. Our data corroborate this, with elevated hexadecanoic acid and its metabolites—oxirane, tetradecyl-, and hexanoic acid, 3,5,5-trimethyl-, 2-ethylhexyl ester—detected in both cancerous and control skin areas of patients.

Methyled benzenes, previously reported at elevated levels in melanoma vs. nevi and skin [44], were also unique to cancer sites in our study. These included benzene, 4-ethyl-1,2-dimethyl-; benzene, 1,2,4,5-tetramethyl-; benzene, 1-methyl-3-(1-methylethyl)-; and benzene, 2,4-diisocyanato-1-methyl. Given prior findings and structural variability, this may be coincidental.

Phthalic compounds, such as bis(2-ethylhexyl) phthalate and phthalic acid, isobutyl 4-octyl ester, have been linked to melanoma and may derive from anthracycline metabolism. We observed similar compounds at elevated levels in cancer samples, supporting prior studies where contamination was excluded [45].

In summary, our results support the use of VOC profiling in cancer detection and validate DC/HS-SPME-GC-MS as a reliable, non-invasive method for identifying skin cancer biomarkers.

5. Conclusion

Our developed DC/HS-SPME technique was shown to provide a demonstrable increase in the VOC signal when compared to a range of alternative approaches for collecting VOCs from skin cancer lesions. DC/HS-SPME should be considered when there is a requirement to assess headspace VOC profiles from skin cancers. The technique was able to retain a variety of VOCs which remained stable for a minimum of 24 h, and was convenient and comfortable for patients. Hexadecanoic acid was the most frequently discovered compound in the skin cancer group. Several other discovered VOCs warrant further investigation. DC/HS-SPME is a newly developed modification of the classic SPME process and represents a novel, non-invasive sampling approach for VOC collection from skin cancer patients in situ.

CRediT authorship contribution statement

Velupillai Ilankovan: Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Richard Paul:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Huseyin Dogan:** Writing – review & editing, Writing – original draft, Funding acquisition. **Santanu Majumder:** Writing – review & editing, Writing – original draft. **Ramin Boroujerdi:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Libby Cowling:** Writing – review & editing, Methodology, Data curation. **Beatriu Asamoa:** Writing – review & editing, Writing – original draft, Validation, Methodology, Formal analysis. **James Dray:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis.

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Table 2
VOCs *only* present in the sampled control area from skin cancer patients.

Patient	Molecular Identity	Retention time (min)	SCC	BCC	Melanoma
12 (SCC)	(2,6,6-Trimethylcyclohex−1-enyl)methanesulfonylbenzene	24.90	✓		
1 (SCC)	1,6-Octadien−3-ol, 3,7-dimethyl-, formate	15.61	✓		
13(SCC)	Piperidine, N-[4-bromo-n-butyl]-	12.39	✓		
9 (Melanoma)	1-Dodecanamine, N,N-dimethyl-	21.59			✓
7 (SCC)	1-Eicosanol	30.5	✓		
1 (SCC)	1-Penten−3-one, 1-(2,6,6-trimethyl−1-cyclohexen−1-yl)-	24.17	✓		
2 (SCC)	2-(4a,8-Dimethyl−6-oxo−1,2,3,4,4a,5,6,8a-octahydronaphthalen−2-yl)propionaldehyde	24.21	✓		
8 (SCC)	2-Azido−2,4,4,6,6-pentamethylheptane	9.51	✓		
1 (SCC)	2-Buten−1-ol, 2-ethyl−4-(2,2,3-trimethyl−3-cyclopenten−1-yl)-	22.04	✓		
14 (BCC)	2H-Benzimidazol−2-one, 1,3-dihydro−5-methyl-	19.60		✓	
14 (BCC)	2-Hexyloctanol	20.5		✓	
7 (SCC)	2-Hydroxyisobutyrophenone	18.2	✓		
17 (SCC)	2-Piperidine, N-[4-bromo-n-butyl]-	12.39	✓		
12 (SCC)	2-Piperidine, N-[4-bromo-n-butyl]-	12.39	✓		
20 (SCC)	2-Propanal, 1-(2-methoxy−1-methylethoxy)-	14.0	✓		
1 (SCC)	2-Propenoic acid, 3-(4-methoxyphenyl)-, 2-ethylhexyl ester	26.5	✓		
4 (SCC)	3,3-Dimethyl−1-(6-methyltetrahydropyran−2-yl)butan−2-one	15.90	✓		
15 (SCC)	4a(2 H)-Naphthalenemethanol, octahydro-	23.5	✓		
15 (SCC)	5,9-Undecadien−2-one, 6,10-dimethyl-, (*E*)-	20.56	✓		
1 (SCC)	7-Acetyl−6-ethyl−1,1,4,4-tetramethyltetralin	27.51	✓		
4 (SCC)	7-Acetyl−6-ethyl−1,1,4,4-tetramethyltetralin	27.51	✓		
16 (SCC)	9-methylheptadecane	14.15	✓		
4 (SCC)	Acetic acid, 1,7,7-trimethyl-bicyclo[2.2.1]hept−2-yl ester	16.41	✓		
6 (BCC)	Azulene	13.9		✓	
5 (BCC)	Azulene	13.9		✓	
9 (Melanoma)	Benzaldehyde, 3-hydroxy-	18.50			✓
4 (SCC)	Benzene, (1-butylheptyl)-	23.60	✓		
4 (SCC)	Benzene, (1-butyloctyl)-	25.41	✓		
4 (SCC)	Benzene, (1-methyldecyl)-	24.84	✓		
4 (SCC)	Benzene, (1-pentylheptyl)-	25.33	✓		
4 (SCC)	Benzene, (1-pentylhexyl)-	23.53	✓		
4 (SCC)	Benzene, (1-propylheptyl)-	21.88	✓		
4 (SCC)	Benzene, (1-propylnyl)-	20.1	✓		
4 (SCC)	Benzene, (1-propyloctyl)-	23.78	✓		
5 (BCC)	Benzene, 2,4-diethyl−1-methyl-	12.95		✓	
5 (BCC)	Benzene, 2-ethyl−1,4-dimethyl-	10.77		✓	
4 (SCC)	Benzenemethanol, α-methyl-, acetate	17.8	✓		
4 (SCC)	Benzoic acid, tetradecyl ester	32.90	✓		
4 (SCC)	Benzoic acid, tridecyl ester	34.38	✓		
4 (SCC)	Bicyclo[2.2.1]heptan−2-one, 1,7,7-trimethyl-, (1S)-	12.96	✓		
5 (BCC)	Carane, 4,5-epoxy-, trans	12.07		✓	
18 (BCC)	Cholesterol	40.68		✓	
6 (BCC)	cis−13-Eicosenoic acid	36.5		✓	
3 (SCC)	Dodecanoic acid	34.0	✓		
6 (BCC)	Dodecanoic acid	34.0		✓	
4 (SCC)	Eicosyl benzoate	37.17	✓		
2 (SCC)	Estra−1,3,5(10)-trien−17beta-ol	30.25	✓		
9 (Melanoma)	Ethyl 4-hydroxymandelate, 2TMS derivative	13.76			✓
4 (SCC)	Eucalyptol	10.06	✓		
4 (SCC)	Indan−1,3-diol monopropionate	19.2	✓		
2 (SCC)	i-Propyl 12-methyltridecanoate	33.2	✓		
19 (BCC)	Octan−2-yl palmitate	37.65		✓	
4 (SCC)	Octanoic acid, 6-ethyl−3-octyl ester	35.0	✓		
4 (SCC)	o-Menthan−8-ol	15.95	✓		
4 (SCC)	ortho tert-Butyl cyclohexyl acetate	16.55	✓		
19 (BCC)	Oxirane, tetradecyl-	13.25		✓	
15 (SCC)	Oxirane, tetradecyl-	13.25	✓		
17 (SCC)	Oxirane, tetradecyl-	13.25	✓		
1 (SCC)	Phenol, m-tert-butyl-	16.2	✓		
9 (Melanoma)	Phthalic anhydride	17.54			✓
11 (BCC)	p-Mentha−1,5,8-triene	11.25		✓	
20 (SCC)	trans-β-Ocimene	8.01	✓		
9 (Melanoma)	Tridecanal	21.73			✓
4 (SCC)	α-Ionone	24.51	✓		

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Richard Paul reports financial support was provided by About Face. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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