**SUPPLEMENTARY MATERIALS:**



***Fig S1****: Temporal dynamics of VOC composition in the urine of a) cancerous (CC) and b) non-cancerous mice (NC) throughout the experiment (T0–T12). Notice the larger variation in VOC profiles for CC compared to NC, and the non-linear of responses of both NC and CC.*

***Table S1****: Summary of the relative proportions of compounds found in the two CC (cancerous) mice that did not develop lung cancer following 12 weeks of doxycycline treatment compared to CC mice having developed lung cancer and NC (non-cancerous) mice. Only the analysis of urine samples collected at T12 are presented here. The eight compounds found to discriminate between non-cancerous and cancerous mice with the full data set are shown in bold.*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Compound | Mouse 1  | Mouse 2  | NC(%, mean ± se) | CC(%, mean ± se) |
| Butan-2-one | 5.9 | 5.3 | 7.49 ± 1.96 | 4.68 ± 1.10 |
| **3-methylButan-2-one** | **6.7** | **2.7** | **2.16 ± 0.32** | **1.15 ± 0.12** |
| **Pentan-2-one** | **7.9** | **2.8** | **3.86 ± 0.64** | **1.58 ± 0.10** |
| 4-methylPentan-2-one | 2.2 | 0.6 | 0.84 ± 0.17 | 0.26 ± 0.05 |
| 3-methylPentan-2-one | 3.8 | 0.9 | 1.37 ± 0.34 | 0.71 ± 0.11 |
| 3-methylcycloPentanone | 1 | 3.5 | 2.40 ± 0.24 | 2.09 ± 0.15 |
| **Hept-4-en-2-one** | **7.1** | **3.5** | **3.78 ± 0.73** | **1.23 ± 0.24** |
| 2-acetyl-1-Pyrroline | 3.4 | 0.6 | 1.18 ± 0.28 | 0.57 ± 0.23 |
| **6-methylHeptan-3-one** | **1.9** | **0.6** | **1.67 ± 0.44** | **3.05 ± 0.44** |
| 3-ethylcycloPentanone | 1.1 | 2.5 | 2.37 ± 0.28 | 2.19 ± 0.26 |
| **4-methylHept-6-en-3-one** | **0** | **0** | **0.01 ± 0.01** | **1.05 ± 0.41** |
| 2,3-dehydro-*exo*-Brevicomine | 0 | 0.13 | 3.76 ± 1.48 | 3.89 ± 1.12 |
| **3,4-dehydro-*exo*-Brevicomine** | **13.2** | **15.4** | **14.22 ± 1.86** | **3.72 ± 0.66** |
| Unknown compound \_10 | 0 | 0 | 1.82 ± 0.59 | 2.05 ± 0.57 |
| Unknown compound \_11 | 0 | 0 | 0.31 ± 0.10 | 0.39 ± 0.13 |
| **2-*Sec*-butyl-4,5-dihydro-Thiazole** | **13.4** | **23.2** | **19.73 ± 3.17** | **38.61 ± 4.88** |
| **Phenylacetone** | **0** | **0** | **0.01 ± 0.00** | **0.32 ± 0.05** |

***Table S2****: VOCs identified in urine samples of cancerous (CC) mice and non-cancerous (NC) control mice. In blue: compounds found only in urine and retained for our analyses. In pink: n-alkanes used as standards to help with the identification of compounds. NI: not identified; RT: retention time; RI: retention index.*

|  |  |  |
| --- | --- | --- |
| **Compound** | **RT** | **RI** |
| n-Hexane | 2.219 | 600 |
| Butan-2-one | 2.383 | 612 |
| Unknown compound 1 | 2.505 | 621 |
| 3-Methylbutan-2-one | 2.987 | 656 |
| Pentan-2-one | 3.365 | 684 |
| NI | 3.548 | 697 |
| n-Heptane | 3.630 | 700 |
| Unknown compound 2  | 3.727 | 706 |
| 2,4-Dimethylfuran | 3.798 | 709 |
| 2,4-Dimethylfuran | 3.855 | 712 |
| NI | 3.925 | 715 |
| 2-Methylbutanenitrile | 3.943 | 716 |
| 2-Methylbutanenitrile | 4.052 | 721 |
| NI | 4.072 | 722 |
| Unknown compound 3 | 4.138 | 725 |
| 4-Methylpentan-2-one | 4.322 | 733 |
| 3-Methylpentan-2-one | 4.6 | 745 |
| Hexan-3-one | 5.33 | 778 |
| Hexan-2-one | 5.452 | 783 |
| NI | 5.677 | 793 |
| NI | 5.737 | 796 |
| n-Octane | 5.829 | 800 |
| 2-Ethyl-hex-2-enal | 6.066 | 808 |
| Unknown compound 4 | 6.265 | 815 |
| Unknown compound 5 | 6.327 | 817 |
| NI | 6.445 | 822 |
| NI | 6.700 | 830 |
| NI | 6.868 | 836 |
| 3-Methylcyclopentanone  | 6.995 | 841 |
| Unknown compound 6 | 7.318 | 852 |
| NI | 7.565 | 861 |
| Heptan-4-one | 7.777 | 868 |
| Unknown compound 7  | 7.933 | 874 |
| Bis(methylthio)methane | 8.192 | 883 |
| Heptan-3-one | 8.197 | 883 |
| Heptan-2-one | 8.312 | 887 |
| Hept-4-en-2-one | 8.467 | 892 |
| NI | 8.558 | 895 |
| NI | 8.568 | 896 |
| NI | 8.598 | 897 |
| NI | 8.665 | 899 |
| n-Nonane  | 8.688 | 900 |
| NI | 8.845 | 905 |
| NI | 8.917 | 907 |
| Unknown compound 8 | 8.925 | 908 |
| (Z)-Pent-2-enyl acetate | 9.028 | 911 |
| NI | 9.037 | 911 |
| NI | 9.122 | 914 |
| NI | 9.128 | 914 |
| 2,6-Dimethylpyrazine | 9.133 | 914 |
| NI | 9.172 | 915 |
| 2-Acetyl-1-pyrroline | 9.272 | 919 |
| NI | 9.558 | 928 |
| ('E)-Hept-3-en-2-one | 9.752 | 934 |
| NI | 10.185 | 948 |
| NI | 10.198 | 948 |
| 6-Methylheptan-3-one | 10.253 | 950 |
| 3-Ethylcyclopentanone | 10.323 | 952 |
| NI | 10.473 | 957 |
| NI | 10.562 | 960 |
| 4-Methylhept-6-en-3-one | 10.793 | 967 |
| Dihydro-3,5-dimethyl-2(3H)-furanone | 11.140 | 978 |
| NI | 11.273 | 982 |
| NI | 11.323 | 984 |
| NI | 11.325 | 984 |
| NI | 11.332 | 984 |
| 4-Methyl-Hept-6-en-3-one | 11.528 | 991 |
| Octanal | 11.815 | 1000 |
| n-Decane | 11.824 | 1000 |
| NI | 12.252 | 1014 |
| Unknown compound 9  | 12.35 | 1017 |
| 2-Ethylhexan-1-ol | 12.747 | 1030 |
| 2-Ethylhexan-1-ol | 12.77 | 1030 |
| Limonene | 12.723 | 1029 |
| 1,8-Cineole | 12.787 | 1031 |
| NI | 12.800 | 1031 |
| 2,3-dehydro-*exo*-Brevicomine | 13.073 | 1040 |
| NI | 13.165 | 1043 |
| 3,4-dehydro-*exo*-Brevicomine | 13.327 | 1048 |
| NI | 13.633 | 1058 |
| NI | 13.637 | 1058 |
| Unknown compound 10 | 13.792 | 1063 |
| Acetophenone | 13.820 | 1064 |
| NI | 13.898 | 1066 |
| NI | 13.982 | 1069 |
| NI | 13.998 | 1070 |
| Unknown compound 11 | 14.345 | 1081 |
| NI | 14.468 | 1085 |
| NI | 14.493 | 1085 |
| NI | 14.618 | 1089 |
| Linalool | 14.94 | 1100 |
| n-Undecane | 14.947 | 1100 |
| Nonanal | 14.982 | 1101 |
| 2-s*ec*-butyl-4,5-dihydro-Thiazole | 15.058 | 1104 |
| NI | 15.343 | 1113 |
| Methyl(methylthio)methyldisulfide | 15.647 | 1123 |
| Phenylacetone | 15.702 | 1125 |
| NI | 16.302 | 1145 |
| alpha-Terpineol | 17.707 | 1192 |
| n-Dodecane | 17.942 | 1200 |
| Decanal | 18.028 | 1203 |
| 2-AminoBenzaldehyde | 18.348 | 1214 |
| n-Tridecane | 20.777 | 1300 |
| Undecanal | 20.917 | 1305 |
| NI | 21.542 | 1329 |
| NI | 21.825 | 1339 |
| n-Tetradecane | 23.448 | 1400 |
| ('E)-beta-Farnesene | 24.930 | 1459 |
| NI | 25.147 | 1467 |
| n-Pentadecane | 25.971 | 1500 |
| (E,E)-alpha-Farnesene | 26.198 | 1510 |
| n-Hexadecane | 28.356 | 1600 |
| n-Heptadecane | 30.431 | 1700  |

***Table S3****: Complete list of VOCs found in the urine of non-cancerous (NC) and cancerous (CC) mice over the 12 weeks of treatment, with their frequencies of occurrence, retention times (RT), retention indices (RI), and references to other studies reporting detection of these molecules in mice or humans. The total number of mice tested per treatment period is in parentheses. The evolution of compounds in cancer patients identified in the literature are indicated with an arrow that increases or decreases.*

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Compound  | T0 | T2 | T4 | T6 | T8 | T10 | T12 | References |
| NC (10) | C (8)  | NC (10) | C (8)  | NC (10) | C (8)  | NC (10) | C (8)  | NC (9)  | C (8) | NC (10) | C (8)  | NC (10) | C (8)  | Studies involving house mice | Studies targeting cancer in house mice | Studies targeting cancer in human |
| Butan-2-one | 10 | 8 | 10 | 8 | 10 | 8 | 10 | 8 | 9 | 8 | 10 | 8 | 10 | 8 | Faeces: [32] Urine: [33,34,64] |  | Breast, colorectal, and lung cancer Urine [42]↗Exhaled breath gastric cancer: [43]↘Leukaemia culture cells: [44]↘ Lung cancer Exhaled breath: [35–41]↗[45]↘[73]appaerTissue: [38,40]↗Cell culture: [46]↘[35,41,67]↗ |
| Unknown compound \_1 | 6 | 3 | 4 | 4 | 8 | 4 | 10 | 2 | 6 | 5 | 8 | 5 | 6 | 2 |  |  |  |
| 3-methylButan-2-one | 10 | 8 | 10 | 8 | 10 | 8 | 10 | 8 | 9 | 8 | 10 | 8 | 10 | 8 | Urine: [34] |  | Head and neck salivary: [72] appaer |
| Pentan-2-one | 10 | 8 | 10 | 8 | 10 | 8 | 10 | 8 | 9 | 8 | 10 | 8 | 10 | 8 | Urine: [33,34,64] | Urine, Breast cancer: [69]↗Cell culture, colorectal cancer: [70]↘Urine, Melanoma:[66]↗  | Breast cancer cell culture: [83] appearLiver cell culture: [74]↗Lung cancer:Exhaled breath [40,75]↗ [35]↘Cell culture: [67,76]↗Bladder: [71]↗ |
| Unknown compound \_2 | 8 | 6 | 8 | 5 | 10 | 6 | 10 | 6 | 9 | 6 | 10 | 8 | 9 | 4 |  |  |  |
| 2-methylButanenitrile | 10 | 8 | 10 | 8 | 10 | 8 | 10 | 8 | 9 | 8 | 10 | 8 | 10 | 8 |  |  |  |
| Unknown compound \_3 | 9 | 6 | 8 | 8 | 8 | 7 | 8 | 8 | 7 | 8 | 9 | 8 | 10 | 8 |  |  |  |
| 4-methylPentan-2-one | 10 | 8 | 10 | 8 | 10 | 8 | 10 | 8 | 9 | 8 | 10 | 8 | 10 | 8 | Urine: [56,58]  |  | Colorectal cancer exhaled breath: [77,78] ↗Bladder:[71]↗  |
| 3-methylPentan-2-one | 10 | 8 | 10 | 8 | 10 | 8 | 10 | 8 | 9 | 8 | 10 | 8 | 10 | 8 | Urine: [56] | Urine, Breast cancer: [69]↘ | Lung cancer, exhaled breath: [79]↗ |
| Hexan-3-one | 10 | 8 | 10 | 8 | 10 | 8 | 10 | 8 | 9 | 8 | 10 | 8 | 10 | 8 | Urine: [56,64,80]  |  | Lung cancer, urine: [42]↗  |
| Hexan-2-one | 10 | 8 | 10 | 8 | 10 | 8 | 10 | 8 | 9 | 8 | 10 | 8 | 10 | 8 | Urine: [56,80] | Urine, Breast cancer: [69] ↗ | Lung cancer, Exhaled breath: [81]↗Cell culture: [67]↗Tissue: [82]↘Colorectal cancer faeces:[83]↗  |
| 2-ethyl-Hex-2-enal | 10 | 8 | 10 | 8 | 10 | 8 | 10 | 8 | 9 | 8 | 10 | 8 | 10 | 8 |  |  |  |
| Unknown compound\_4 | 7 | 6 | 8 | 6 | 7 | 5 | 7 | 6 | 3 | 5 | 8 | 6 | 7 | 6 |  |  |  |
| Unknown compound\_5 | 10 | 8 | 10 | 8 | 10 | 8 | 10 | 8 | 9 | 8 | 10 | 8 | 10 | 8 |  |  |  |
| 3-methylcycloPentanone  | 10 | 8 | 10 | 8 | 10 | 8 | 10 | 8 | 9 | 8 | 10 | 8 | 10 | 8 |  |  |  |
| Unknown compound, \_6 | 10 | 8 | 10 | 8 | 9 | 8 | 10 | 8 | 8 | 8 | 10 | 8 | 9 | 8 |  |  |  |
| Heptan-4-one | 9 | 8 | 9 | 8 | 10 | 8 | 10 | 8 | 9 | 8 | 10 | 8 | 10 | 8 | Urine: [56] |  | Lung cancer, exhaled breath: [75] appaer Colorectal and breast cancer, urine: [84]↗Bladder: [71]↘ |
| Unknown compound \_7 | 10 | 8 | 10 | 8 | 10 | 8 | 10 | 8 | 9 | 8 | 10 | 8 | 10 | 8 |  |  |  |
| Heptan-3-one | 3 | 4 | 3 | 7 | 9 | 7 | 8 | 8 | 9 | 8 | 8 | 8 | 6 | 8 | Urine: [56] | Urine, Breast cancer: [69]↗Cell culture, colorectal cancer: [70]↗ | Breast cancer, urine [85]↗Colorectal leukemia, urine: [86] DisappearLymphoma, urine [86]↗Liver cell culture: [74]↗Lung cancer, Exhaled breath: [81]↗Urine: [87]↗ |
| Heptan-2-one | 10 | 8 | 10 | 8 | 10 | 8 | 10 | 8 | 9 | 8 | 10 | 8 | 10 | 8 | Urine: [33,34,56,58,64,88–92]  | Urine lung cancer: [17]Blood Colorectal cancer [93]↗Cell culture colorectal cancer: [70]↗ | Breast cancer, urine [85] appaerLiver cell culture: [74]↗Lung cancer, urine: [42]↘ |
| Hept-4-en-2-one | 10 | 8 | 10 | 8 | 10 | 8 | 10 | 8 | 9 | 8 | 10 | 8 | 10 | 8 | Urine: [33] |  |  |
| Unknown compound \_8 | 10 | 8 | 8 | 8 | 9 | 8 | 10 | 8 | 9 | 8 | 10 | 8 | 10 | 8 |  |  |  |
| 2-acetyl-1-Pyrroline | 10 | 8 | 10 | 8 | 10 | 8 | 10 | 8 | 9 | 8 | 10 | 8 | 10 | 8 | Urine: [33,58,64,65] | Urine, lung cancer: [17]Urine, melanoma: [66]↗ |  |
| ('E)-Hept-3-en-2-one | 8 | 6 | 8 | 8 | 8 | 8 | 9 | 8 | 7 | 8 | 9 | 8 | 8 | 8 | Urine: [57,90,94] |  |  |
| 6-methylHeptan-3-one | 10 | 8 | 10 | 8 | 10 | 8 | 10 | 8 | 9 | 8 | 10 | 8 | 10 | 8 | Urine: [64,65,94] |  |  |
| 3-ethylcycloPentanone | 10 | 8 | 10 | 8 | 10 | 8 | 10 | 8 | 9 | 8 | 10 | 8 | 10 | 8 |  |  |  |
| 4-methylHept-6-en-3-one | 1 | 3 | 2 | 6 | 4 | 8 | 5 | 8 | 5 | 8 | 7 | 8 | 3 | 7 | Urine: [65,90] | Melanoma:[66]↗ |  |
| 4-methyl-Hept-6-en-3-one  | 10 | 6 | 10 | 8 | 10 | 8 | 10 | 8 | 9 | 8 | 10 | 8 | 10 | 8 |  |  |  |
| Unknown compound \_9 | 9 | 7 | 10 | 8 | 9 | 8 | 10 | 8 | 9 | 7 | 10 | 7 | 10 | 7 |  |  |  |
| 2,3-dehydro-*exo*-Brevicomine | 9 | 7 | 10 | 7 | 10 | 8 | 10 | 7 | 9 | 7 | 10 | 8 | 9 | 8 |  Urine: [34,88,89]  | Urine, lung cancer:[17] |  |
| 3,4-dehydro-*exo*-Brevicomine | 10 | 8 | 10 | 8 | 10 | 8 | 10 | 8 | 9 | 8 | 10 | 8 | 10 | 8 | Urine: [33,57,58,64,80,90,92,95,96] | Melanoma:[66]↗  |  |
| Unknown compound \_10 | 9 | 6 | 10 | 7 | 10 | 8 | 10 | 6 | 8 | 7 | 10 | 7 | 8 | 7 |  |  |  |
| Unknown compound \_11 | 4 | 3 | 4 | 6 | 9 | 5 | 6 | 5 | 7 | 7 | 7 | 7 | 6 | 6 |  |  |  |
| Linalool | 1 | 2 | 3 | 3 | 5 | 5 | 6 | 5 | 6 | 8 | 5 | 8 | 6 | 7 | Urine: [57,58,94] |  |  |
| 2-s*ec*-butyl-4,5-dihydro-Thiazole | 10 | 8 | 10 | 8 | 10 | 8 | 10 | 8 | 9 | 8 | 10 | 8 | 10 | 8 | Urine:[34,56–58,88–90,92,94,95,97] | Urine lung cancer: [17] ↗  |  |
| Phenylacetone | 4 | 4 | 4 | 7 | 7 | 8 | 7 | 8 | 8 | 8 | 8 | 8 | 7 | 8 | Urine: [57,58,91] |  |  |