# Reply to Turin et al.: Vibrational theory of olfaction is implausible

We thank Turin et al. (1) for their comments regarding our paper (2). In response to the first point of Turin et al. (1), concerning the musk receptor screen, our reported results (2) were directed at testing the main hypothesis of the vibrational theory of olfaction, which has never been supported by experimental data at the receptor level. The negative results of the tests, using one of the best available experimental tools, constitute an important, positive contribution to olfactory science, providing clear experimental evidence against the vibration mechanistic hypothesis in a biological milieu.

Regarding the second point, that an impurity may have affected the odor of Gane et al.'s (3) deuterated musks, it is clear that the presence of the impurity compromises their conclusions. Whether the impurity is responsible for the reported smell difference, or the difference is a result of other effects [e.g., perireceptor processes susceptible to secondary deuterium isotope effects (4)], remains unknown.

Detailed analysis of receptors 296 (OR51E1) and 173 (OR5M9) with an expanded concentration range of cyclopentadecanone isotopomers clearly shows that neither responds to any of the isotopomers: there are no significant differences among H and D isotopomers (Fig. 1). These experiments support our conclusions (2) and invalidate Turin et al.'s conclusion (1) based on an incomplete $t$ test analysis, which was uncorrected for multiple comparisons. When 330 comparisons are performed, up to seven odorant receptors with $P < 0.02$ should be obtained by chance. With a Bonferroni correction for 330 odorant receptors, the raw $P$ value must be <0.000152 to be significant ($P < 0.05$ after correction).

Turin et al. (1) admit to an impurity, shown by NMR, in their deuterated cyclopentadecanone (3), absent in the undeuterated compound. The impurity could compromise their conclusions because neither crystallization nor other standard purification techniques removed it before injection in a heated injection port. The 0.87 ppm impurity integrated area (10.5% total area of residual protons in 90–95% deuterated cyclopentadecanone) represents a substantial level of unknown impurity for an olfactory testing sample, even if GC-purified. Whether or not that impurity or its decomposition products coelute with musks from the GC has not been established. Turin et al's (1) assignment of the 0.87 ppm NMR peak impurity to cyclopentadecane is incorrect: cyclopentadecane has a single peak at 1.327 ppm.* Our peak at 1.26 ppm corresponds to residual protons in cyclopentadecane-$d_{30}$ (2).

Regarding Turin et al.'s (1) third point, the omission of any description of odor character of the deuterated musks we synthesized and tested, our paper (2) is focused on experimental evidence at the molecular level, ruling out the hypothesis that molecular vibrations are essential for activation of odorant receptors. Anecdotal smelling sessions were not included because they are noninformative on the effect of the odorant vibrations on the receptor response. We emphasize that there is a wide gap between positive perception and positive evidence of electron transfer rates modulated by molecular vibrations.

Finally, future in vivo response studies might answer why flies and humans perceive isotopes differently. Isotopomers can produce very different effects on a variety of reaction mechanisms, even when they are indistinguishable for a given receptor (2). For example, perireceptor processes involving nasal mucus are susceptible to secondary deuterium isotope effects (4).

We stress that there is no experimental data at the molecular level showing direct evidence of electron transfer—or the effect of odorant vibrations—being responsible for triggering odorant receptor response.

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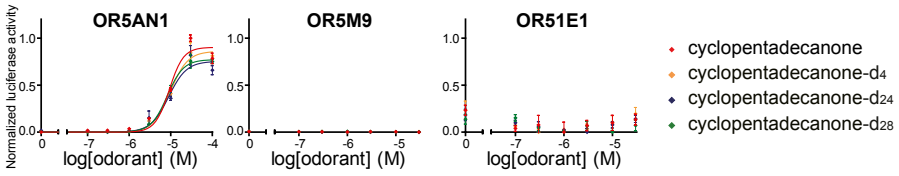


**Fig. 1.** Receptors 296 (OR5M9) and 173 (OR51E1) do not respond to isotopomers of cyclopentadecanone. The response of receptor OR5AN1 is shown as a reference.

**1** Turin L, Gane S, Georganakis D, Maniati K, Skoulakis EMC (2015) Plausibility of the vibrational theory of olfaction. *Proc Natl Acad Sci USA* 112:E3154.

**2** Block E, et al. (2015) Implausibility of the vibrational theory of olfaction. *Proc Natl Acad Sci USA* 112(21):E2766–E2774.

**3** Gane S, et al. (2013) Molecular vibration-sensing component in human olfaction. *PLoS ONE* 8(1):e55780.

**4** Schilling B, Kaiser R, Natsch A, Gautschi M (2010) Investigation of odors in the fragrance industry. *Chemoecology* 20(2):135–147.

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The authors declare no conflict of interest.

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*See sdbs.db.aist.go.jp/sdbs/cgi-bin/cre_search.cgi.