

Guidelines/Criteria	
Reference:	Cometto-Muñiz JE, Cain WS, Hudnell HK. 1997. Agonistic sensory effects of airborne chemicals in mixtures: Odor, nasal pungency, and eye irritation. <i>Percept Psychophys</i> 59(5):665-674.
In vivo Study Type Route of Administration Species & age of animals	Airborne Human, various ages, osmic and anosmic
Study Duration	Series of single tests
Type of Mixture Binary >2 components Similar acting or dissimilar What Mode of Action was investigated?	None 2 three-component mixtures, 2 six-component mixtures, 1 nine-component mixtures Not defined; homologous series of alcohols, esters, ketones and alkyl benzenes were tested Olfactory nerve stimulation (odour), trigeminal nerve stimulation (nasal pungency, eye irritation)
Parameters/End points Measured Target organs/Critical effects Pharmacological changes or adverse effects	Nose (odour, pungency), eye (irritation) Pharmacological (odour), adverse (nasal pungency and eye irritation)
Individual Components Characterisation of individual compounds Name, exact chemical name, CAS no. Were dose responses established for individual components? Were no effect levels established? Were doses below the NO(A)ELs investigated?	Alcohols: 1-propanol, 1-butanol, 1-hexanol Esters: ethyl acetate, hexyl acetate, heptyl acetate Ketones: 2-pentanone, 2-heptanone Alkyl benzenes: toluene, ethyl benzene, propyl benzene Yes Yes (thresholds) Yes
Mixtures Investigated Number of dose levels How does the mixture make-up compare to individual components? (e.g. low dose) equivalents used? No. of technical replicates per exposure condition (<i>in vitro</i>) No. of animals per dose group (<i>in vivo</i>)	Up to 15 dilutions of mixtures in which the maximum possible concentration of chemicals was present.(according to the proportion corresponding to individual thresholds) Mixtures were prepared in proportion of the odour thresholds of individual components; concentrations were varied in three-fold steps above and below the reference concentration Eight thresholds per subject (four for each nostril or eye) for each single compound and each mixture Eight osmic subjects (4m, 4f), age 21 - 60 y Four anosmic subjects (2m, 2f), 20 - 66 y
Observations/Findings	Thresholds for all sensory responses declined with increasing number of components in the mixture. Lipophilicity also enhanced the chemosensory potency of mixtures. For odour, partial agonism was the most frequent interaction, for nasal pungency both partial agonism and agonism were present, for eye irritation showed synergistic action for the most lipophilic and for the most complex mixture.
Overall opinion (e.g. sufficient numbers of groups investigated, group sizes adequate, observations reproducible, low dose levels used investigated)	The number of subjects is relatively small and the procedure is complex; some degree of habituation may be present. Reliance on odour thresholds for single compounds established in previous studies is a limitation, as is the use of a threshold concept rather than concentration-detection functions (see later studies for details). Nevertheless, it is a well-controlled exploratory study which suggests that for sensory irritation effects of mixtures (partial) agonism is the norm, with some synergism suggested for eye irritation.