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Assessment of odour annoyance in chemical emergency management

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Abstract

Assessment of odour annoyance in chemical emergency management

In chemical emergencies the exposed community is likely to interpret the presence of an unusual odour not common to the normal 'odour landscape' as a potential health risk. This report describes a methodology for assessing the airborne concentration level at which the exposed community is likely to become aware of the presence of a chemical by detecting its odour, which in turn may require communicative emergency response activities, even in the absence of toxicological health risks.

The presented methodology will help emergency response organizations to improve the understanding of odour driven public concerns in chemical emergencies, and improve their ability to assess if and which type of response is adequate.

The methodology builds on consensus reached within the Acute Exposure Guideline Levels (AEGL) program that an airborne concentration producing a distinct odour perception in more than half of an accidentally exposed, distracted population would qualify as significant odour awareness. This concentration is designated as 'Level of distinct Odour Awareness (LOA)'. The LOA is determined in three steps:

1. Select an appropriate odour threshold, for instance from one of the suggested sources.
2. Derive a distinct odour level based on the Weber-Fechner equation.
3. Adjust for field circumstances such as age, head cold and the usual exposure pattern.

The LOA must be developed on a chemical-by-chemical basis. The availability of high quality chemical specific information for steps 1 and 2 is a major hurdle, which has been partly overcome by introducing default values.

Key words:
odour annoyance, chemical emergency, emergency response, emergency planning

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Rapport in het kort

Bepaling van geurhinder voor crisisbeheersing

Bij chemische incidenten zal de blootgestelde bevolking de aanwezigheid van een ongebruikelijke geur vaak interpreteren als een mogelijk gezondheidsrisico. Dit rapport beschrijft een methode om de luchtconcentratie te schatten waarbij de blootgestelde bevolking zich bewust wordt van de aanwezigheid van een chemische stof door geur(hinder). Deze waarneming kan communicatie en andere maatregelen nodig maken, zelfs bij afwezigheid van relevante toxische risico's.

De voorgestelde methode zal het begrip bij crisisbeheersers over onrust bij de getroffenen door geurwaarneming vergroten, en hen beter in staat stellen te beslissen wanneer welke crisisbeheersingsmaatregelen wenselijk zijn.

De methode sluit aan bij consensus binnen het Acute Exposure Guideline Levels (AEGL) programma waarin is bepaald dat een concentratie waarbij 50% van een afgeleide incidenteel blootgestelde bevolking een 'duidelijke' geur waarneemt, dit beschouwd wordt als 'duidelijke geurwaarneming'. De luchtconcentratie waarbij dat optreedt heet 'Level of Distinct Odour Awareness (LOA)'. De LOA wordt in drie stappen bepaald:

1. Selecteer een goede geurdrempel, bijvoorbeeld via een van de aangegeven bronnen.
2. Bepaal een niveau van 'duidelijke' geurwaarneming.
3. Verdisconteer veldomstandigheden zoals leeftijd, verkoudheid en blootstellingspatroon.

De LOA moet voor iedere stof apart worden afgeleid. De beschikbaarheid van goede informatie voor de stappen 1 en 2 blijkt in de praktijk beperkend te zijn; deze beperkingen zijn deels omzeild door gebruik van standaardwaarden.

Trefwoorden:
geurhinder, chemisch incident, rampenbestrijding, crisisbeheersing, preparatie

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Summary

One of the most prominent public health roles in a chemical emergency is to assess the risk of acute and delayed health effects due to the chemical exposure and to promote an adequate response, including communication with the community. The usual approach is based on a characterization of actual exposure and determination of toxicological exposure-response (or -effect) relationships for the released chemicals.

In many cases, such a toxicological approach provides clear guidance about the necessary emergency response approach and activities, but may not suffice for releases of chemicals that can be perceived by the pubic and can cause odour annoyance at ambient concentrations well below a threshold for toxicity. This situation will invariably raise questions in the exposed population which may develop into anxiety unless there is clear communication about the source and the nature of the smell and the risk and severity of potential health effects, even when the toxicological assessment may indicate there is no real health risk.

This report describes a methodology for assessing the airborne concentration level at which the exposed community is likely to become aware of the presence of a chemical by detecting its odour, which in turn may require communicative emergency response activities, even in the absence of toxicological health risks.

The methodology builds on consensus reached within the Acute Exposure Guideline Levels (AEGL) program that an airborne concentration producing a distinct odour perception in more than half of an accidentally exposed, distracted population would qualify as significant odour awareness. This concentration is designated as ‘Level of distinct Odour Awareness (LOA)’. The LOA is determined in three steps:

1. Select an appropriate odour threshold, for instance from one of the suggested sources.
2. Derive a distinct odour level based on the Weber-Fechner equation.
3. Adjust for field circumstances such as age, head cold and the usual exposure pattern.

The LOA must be developed on a chemical-by-chemical basis. The availability of high quality chemical specific information for steps 1 and 2 is a major hurdle, which has been partly overcome by introducing default values.

The presented methodology will help local (GHOR, fire brigade) and national (BOT-mi) emergency response organizations to improve the understanding of odour driven public concerns in chemical emergencies, and improve their ability to assess if and which type of response is adequate.

1 The relevance of odour in chemical emergency response

1.1 Risk assessment in chemical emergencies

One of the most prominent public health roles in a chemical emergency is to assess the risk of acute and delayed health effects due to the chemical exposure and to promote an adequate response, including communication with the community (WHO, 2009). The usual approach to such risk assessments is based on a characterization of actual exposure and determination of toxicological exposure-response (or -effect) relationships for the released chemicals. To speed up the assessment process, the initial assessments for airborne releases are often based on exposure estimates from air dispersion modelling and emergency guidelines predicting the severity of the health outcome (for instance AEGL, ERPG).

In many cases, such a toxicological approach provides clear guidance about the necessary emergency response approach and activities. The toxicological approach may not suffice for releases of chemicals that can be perceived by the pubic and can cause odour annoyance at ambient concentrations well below a threshold for toxicity. This situation will invariably raise questions in the exposed population which may develop into anxiety unless there is clear communication about the source and the nature of the smell and the risk and severity of potential health effects, even when the toxicological assessment may indicate there is no real health risk.

This report aims to develop a methodology for assessing the concentration level at which the exposed public is likely to become aware of the presence of a chemical by detecting its odour, which in turn may require communicative emergency response activities, even in the absence of toxicological health risks, to avoid unwarranted anxiousness and community stress.

1.2 Background

Humans, like most creatures, continuously need information on their environment ,in order to survive. They rely on their senses to obtain this information and to assess their environment. All sensory perception is provided to the brain for appraisal and is then used to determine and adapt our behaviour in such a way as to optimize survival.
In simple terms of behaviour, perception of odour can lead to two basic behavioural responses: avoidance or approach (Carter, 1998). These responses can occur for example in judging food or water or air, but also in a social or sexual context. Humans can distinguish thousands of odours and can detect odours of some chemicals at concentrations as low as a few parts per trillion. For example, our nose is very sensitive to certain repulsive-smelling compounds, produced in trace amounts by some bacteria and moulds in rotting processes involving proteins, such as methyl

mercaptan and trimethyl amine. The evolution of a high sensitivity for these odorants may have developed in order to provide early warning to avoid dangerous infection or food poisoning. In general, however, there is no correlation between odorous and toxic properties of chemicals. Some compounds cannot be detected by smell, even when they are present in toxic concentrations (for instance carbon monoxide). Other compounds, such as hydrogen sulphide, trigger a response as a result of their odorous properties, although they are present in concentrations well below toxic levels. In the case of hydrogen sulphide, the character of the perceived odour even changes to more pleasant and eventually becomes less odorous at higher, toxic concentrations (AIHA, 1989). For specific compounds the intensity of the perceived odour provides information about the concentration we are exposed to. If the toxicity threshold is substantially higher than the odour recognition threshold, the intrinsic odour of the compound provides an indication of its presence, at a sufficiently low concentration to avoid harm to the exposed human. Conversely, if the odour recognition threshold is much higher than the toxicity threshold, then anybody detecting the odour of the compound has a warning that a safe concentration has already been exceeded (Amoore,1983).

1.3 Appraisal of odour

The function of our smell sensor is similar to that of all senses: to translate environmental information into electrical signals, transmitted by neurons firing in our brain. This information is then evaluated in the brain, a process broadly termed appraisal (Buck, 2005).
Appraisal is a complex process, involving various parts of the brain. The processing of smell signals differs from other senses, because the olfactory information goes straight to the limbic system – a fast route to the brain's emotional and memory organisation centre. Whether we find a smell nice or nasty depends crucially on the memories that are associated with that particular odour. The same smell may have a positive connotation for one individual and a negative connotation for another (Paduch, 1995; Distel and Hudson, 2001). Appendix 1 provides a little more detail about the organization of the olfactory system.
When an individual detects an unknown odour and is not provided with any information about the odour source (and potential adverse effects), the ensuing appraisal is likely to be negative. Such negative appraisals lead to hyper-vigilance and arousal, which can result in a cascade of autonomic symptoms, including altered respiration (often to minimize odour perception), increases in heart rate, feelings of dizziness or throat or chest tightness (Shusterman, 1992; Dalton, 1997). Paradoxically, the very same effects that are generated as a result of the negative appraisal by the individual are then perceived as and attributed to a direct physiological effect of the chemical exposure, unless information to the contrary is provided from a trusted source. The concentrations at which these adverse appraisal effects occur will be significantly modulated by regular exposure leading to habituation, such as occurs in the workplace (Wysocki et al., 1997, Smeets and Dalton, 2002). Thus, it is possible that concentrations that generate concern in a community will not be of consequence or significance in an occupational setting. Detectable and recognisable concentrations that may generate alarm in a community are not necessarily at toxicologically significant levels.

They do, however, represent concentrations where notification (i.e., informing the public about properties of the unusual odour) is recommended to positively modulate appraisal of the odour and thus prevent or reduce unnecessary anxiety and stress-related health effects.
This document aims to provide scientific underpinning of a 'Level of distinct Odour Awareness' (LOA) in accidental chemical exposure of the general population. This LOA can be used to estimate in which locations members of the public are likely to become sufficiently anxious to call the emergency services or environmental complaint response services in significant numbers ('telephone zone'). The ability to predict the 'telephone zone' enables the emergency response system to make informed decisions about communication to the public. Such information is crucial for emergency response organizations.

1.4 Scope of this report

This report is aimed at public health professionals and toxicologists involved in chemical emergency planning and response or in the derivation of emergency guidelines to assess possible health outcomes of acute inhalation exposures in the general population (such as AEGL and ERPG).
The authors have explored the scientific basis for making use of odour characteristics in determining the emergency response to chemical incidents. More specifically this report aims to develop a methodology for assessing the concentration level at which the exposed general population is likely to become aware and potentially alarmed about the presence of a chemical due to odour detection (or rather: annoyance).

2 Odour detection

Four major attributes can characterise the sensory perception of odorants: detectability, intensity, hedonic tone and odour quality.
Because there are no instrumental methods that predict the responses of our sense of smell to a satisfactory degree, the human nose is the most suitable 'sensor'. Olfactometry employs a panel of human noses as sensors.

Figure 1: Dynamic olfactometry with human assessors, to measure odour concentration according to EN13725. Photo courtesy of Odournet UK Ltd.

2.1 Detectability

Detectability is the most common attribute used to characterize odours. Detectability refers to the minimum concentration of odorant necessary for detection by some specified percentage of the test population. In chemosensory detection, other pathways may contribute, such as the trigeminal nerve (irritation) and the vomeronasal organ. Using panelist responses over a range of concentrations, the odour threshold concentration can be assessed. The variability and likelihood of detection both within and between individuals plays a role:

1. As with any psychophysiological measurement (odour, hearing, sight, vibration, et cetera), the likelihood of an individual to detect a signal is related to the stimulus intensity. In this case, the likelihood that an individual will smell the chemical is related to its airborne concentration. An individual's odour threshold is usually defined as the concentration where this likelihood is 50% (cf. left part of Figure 2, Cometto-Muñiz and Abraham, 2008).
2. The population odour detection threshold is the airborne concentration at which 50% of the population can smell the odorant. This odour threshold is usually determined by a limited number of panelists in an olfactometry experiment (cf. right part of Figure 2). At the odour threshold (ODT), the odour concentration of an odour sample (single compound or mixture) is defined to be 1 odour unit per cubic meter. In modern olfactometry standards (EN13725:2003, AS/NZS4323.3:2001,) the odour unit is linked to a specific concentration of a reference odorant, such as 1 ou_E/m^3 (European Odour Unit) ≡ 40 ppb/v *n*-butanol. The relation is implemented by selecting a sample from the population of assessors with olfactory sensitivity close to that agreed reference value.

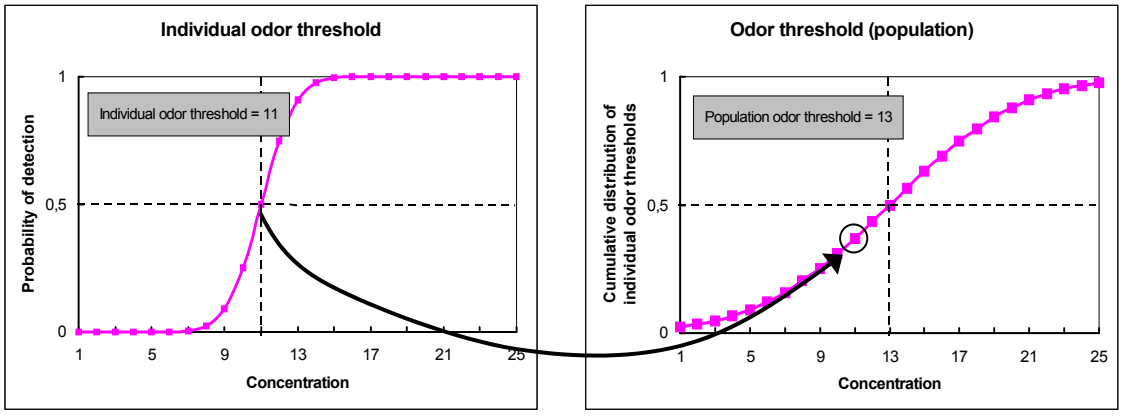

Figure 2: Individual and group odour detection thresholds.

The way in which the response of our sense of smell is reduced to a single value of a parameter amounts to a gross simplification of the rich spectrum of sensory information that is actually perceived by the brain. Such a simplification may be useful, however, in describing potential effects. The reduction of a very complex physiological process to a simple parameter is methodologically very similar to expressing the effects of toxic substances on an organism as the LC_{50}, which indicates the concentration causing lethality in 50% of a well-defined test population under well-defined test conditions. The complex physiological response is regarded as the unifying reaction that can be caused by a wide range of substances, at an equally wide range of concentrations.

The inter-individual variability of odour detectability is known to be very large. Given the typical size of an odour panel (6-10 individuals), such a sample cannot be expected to represent the general population adequately. The mere choice of the sample of assessors forming the panel may introduce a large bias in the measured odour threshold. There are two ways out of this dilemma:

1. Use very large odour panels (hundreds of people); this is regarded to be impractical.
2. Standardize the test subjects to assess the sensory response without introducing a bias (EN13725:2003, Van Harreveld et al., 1998).

Reproducible results can be obtained by selecting panel members with a known sensitivity to an accepted reference material (currently *n*-butanol). The assumption underlying this method is that the sensitivity for the reference odorant will predict the sensitivity to other substances. However, just as olfactory sensitivity can vary widely across a population to the same chemical, olfactory sensitivity to different chemical compounds can vary dramatically within the same individual. In other words, the sensitivity to a single chemical can never serve as a fully satisfactory predictor for sensitivity to all chemicals in an individual assessor. The approach benefits from the use of a number of assessors in a panel, and excluding those with aberrant responses in a retrospective screening process, that is applied to each dataset underlying a test result according to EN13725:2003. The use of at least one internal standard has proven the most effective step forward in improving reproducibility compared to not using a referent compound at all. Its

effectiveness has been demonstrated in practice in interlaboratory testing (Van Harreveld et al., 1998). In modern olfactometry standards, the odour unit is therefore linked, through selection of assessors, to a reference odorant concentration (e.g.1 $ou_E/m^3 \equiv 40$ ppb/v *n*-butanol in EN13725:2003 and AS/NZS4323.3:2001). It is very encouraging that there is such an excellent agreement in data obtained from Dutch and Japanese studies (Hoshika et al., 1993, Annex 3). Appendix 2 provides more detailed information about olfactometry.

2.2 Intensity

Intensity is the second dimension of the sensory perception of odorants and refers to the perceived strength or magnitude of the odour sensation. Intensity increases as a function of concentration. The relation between perceived intensity and the *logarithm* of odour concentration is linear. The relationship between perceived intensity *I* and stimulus concentration may be described as a theoretically derived logarithmic function according to Fechner:

$$I = k_w \cdot \log(C/ODT) + 0.5$$

where

I	perceived intensity of sensation (on intensity scale)
C	odour concentration in ppb
ODT	population odour detection threshold concentration in ppb
k_w	Weber-Fechner coefficient

The preferred method for measuring intensity is derived from the German standard VDI3882 Part 1 (1992). The principle of measurement is the presentation of odour to human assessors in an odour panel, at varying degrees of dilution, hence varying perceived intensity. The members of the panel are asked to indicate perceived intensity at each presentation as a value *I* on an ordinal seven point intensity scale:

0 no odour
1 very faint odour
2 faint odour
3 distinct odour
4 strong odour
5 very strong odour
6 overwhelming odour

The values for *I* are then plotted against the logarithm of the odour concentration or the dilution factor. The regression line characterizes the relation between perceived intensity and odour concentration. The point where the regression line intersects with the horizontal axis is approximately equivalent to the detection threshold. For example, the regression equation for menthone was:

$I = 2.35 \log C - 2.24$ ($r^2 = 0.98$) with C = concentration in ppb

From this it may be calculated that a distinct menthone odour (I=3) was perceived at a concentration of 170 ppb.

The Fechner model assumes that the intensity coefficient is constant over the whole exposure range. This assumption may hold below the chemesthetic (irritation) threshold, the slope will likely increase once that threshold is exceeded. In intensity variation studies of pure substances the following k_w values were found with the standard method VDI 3882, Part 1: *n*-butanol 1.9 (1.65 and 2.1) iso-amyl alcohol 2.2; hydrogen sulphide 2.2 (1.9, 2.33 and 2.41); acetone 2.3; menthone 2.35; guiacol 2.66; methylacrylate 2.7; and ammonia 3.5. The range is surprisingly small with a median value of 2.33. The high value for ammonia may be the result of chemesthetic receptor involvement. Odorants with high slope values, such as ammonia dissipate quickly with dilution. Odours with lower slope values, such as *n*-butanol are more difficult to control.

2.3 Hedonic tone

Hedonic Tone is the third dimension of odour (AIHA, 1989; US EPA, 1992). This is a category judgement of the relative like (pleasantness) or dislike (unpleasantness) of the odour. The method for measuring hedonic tone is derived from a German standard method VDI 3882, Part 2 (1994). The principle of measurement is presentation of the odour to human assessors in an odour panel, at varying degrees of dilution. The members of a panel of assessors are requested to indicate the perceived hedonic tone as a value from the nine-point hedonic tone scale:

+4	very pleasant
+3	pleasant
+2	moderately pleasant
+1	mildly pleasant
0	neutral odour / no odour
-1	mildly unpleasant
-2	moderately unpleasant
-3	unpleasant
-4	offensive

In contrast to the small inter-individual variation in the perceived intensity of a certain odorant concentration, the inter-individual variation in hedonic perception is substantial, among other factors dependant on odour experience, education and cultural setting (Paduch, 1995; Distel and Hudson, 2001).
For each concentration level, the mean of the values for H of all panel members is calculated, and plotted against the odour concentration. A fictitious example of the plotted result is presented in Figure 3. Using a suitable curve fitting procedure a line can be fitted through the points obtained in the experiment. Using this interpolation, characteristic values can be derived from the plot, such as the odour concentration at H = -2.

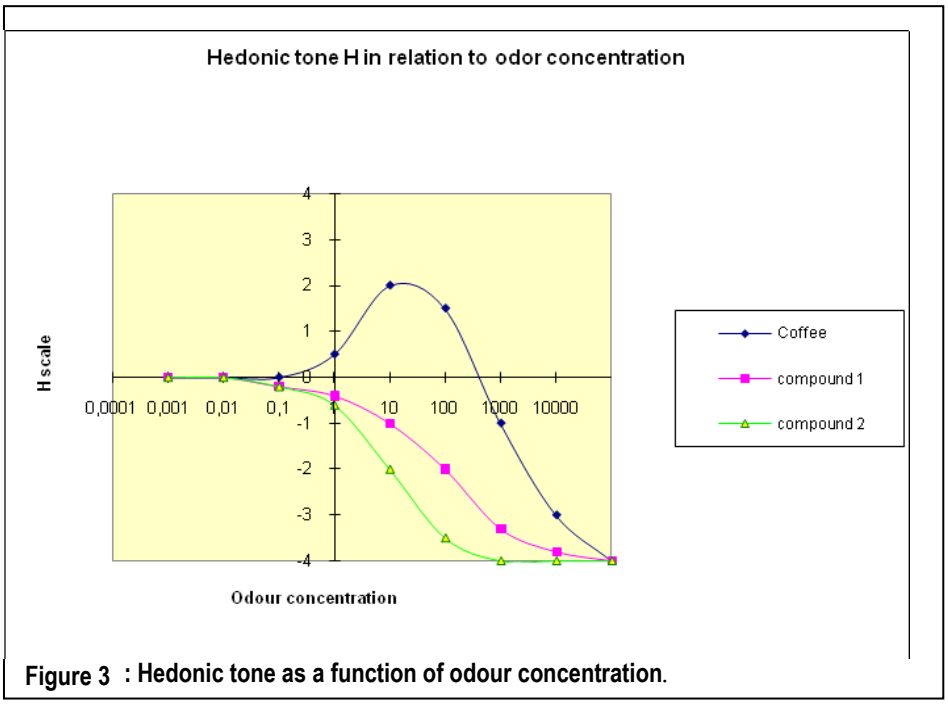

Figure 3 : Hedonic tone as a function of odour concentration.

There is no simple general relationship between intensity and hedonic tone. For example, a number of odorants (pure substances as well as mixtures) were diluted to reach strong odour detection ($I = 4$) in an odour panel (Winneke et al., 1995). Subsequently, the members of the panel were asked to estimate the hedonic tone. The results are shown in Table 1. Some strong odours (pine, menthone) were perceived as neutral or pleasant. Other strong odours (sulphur disulphide) were perceived as moderately to clearly unpleasant.

Table 1 : Hedonic perception of odorant concentrations at strong intensity level (Winneke 1995).

Hedonic value	Hedonic description	Odour quality
$H = > 0$	Neutral or pleasant	Pine, menthone, perfume, bakery
$H = < 0$ and > -1	Neutral to mildly unpleasant	Amylacetate, thinner, butanol
$H = < -1$ and > -2	Mildly to moderately unpleasant	Chlorine, perchloroethylene, biofilter
$H = < -2$ and > -3	Moderately to clearly unpleasant	Pig house, sulfur disulfide, teflon melting

Distel and Hudson (2001) found that ratings for pleasantness for 24 everyday odorants increased when subjects could identify the odour source themselves or were provided with the name by the investigator. Ratings were highest when subjects judged that the names provided by the

investigators matched their own perception, suggesting an interaction between individuals' cognitive representation of odours and their immediate perceptual experience.

2.4 Odour quality

Odour quality is the fourth dimension of odour. It is expressed in descriptors, i.e. words that describe what the substance smells like. This is a qualitative attribute, expressed in words, such as *fruity, fishy, hay, nutty*. The American Society for Testing and Materials (ASTM) developed a list of 146 descriptors and used it to characterize 160 compounds and mixtures in a standardized manner, with a large panel of 120-140 individuals. The results are published in an 'Atlas of Odour profiles' (ASTM, 1968).
In an alternative approach, a formal set of descriptors is arranged in an 'odour wheel' to characterize a specific domain of odorants, for instance to evaluate off flavours in drinking water or to characterise sensory attributes of wines. (Suffet and Rosenfeld, 2007)
The character of an odour may change with concentration level. For example, hydrogen sulphide at levels of 20 ppm or above ceases to be perceived as the typical 'rotten egg' smell and its perceived odour at these elevated concentrations will be described as 'sweet'. At even higher concentrations, which are acutely toxic, hydrogen sulphide becomes odourless.
A special area in odour quality is *masking*. When an odour is unpleasant, strong odours are usually considered 'pungent', not just strong. Deodorants may affect the quality (pleasantness) of the overall just because they mix with the malodours (Ruth, 1986). The mixtures of the smells may be perceived to be less intense or of a different character and hence less unpleasant than the original malodour.

3 Irritation, somatic symptoms and annoyance

3.1 Irritation

Some chemicals, besides having a true odour, also cause immediate irritation of the eyes, throat and nose. The sensation of stinging, prickling, or burning, mediated by the trigeminal or 5th cranial nerve, is quite distinct from the smell sensation carried out by the olfactory or 1st cranial nerve (Figure 4). The free nerve endings of the trigeminal nerve are located over the nasal, oral, and ocular *mucosae.* Stimulation of the trigeminal nerve in the nose produces chemical irritation (Cain and Murphy, 1980; Dalton, 2003; Doty et al., 2004; Arts et al., 2006). Irritation combines with olfaction to form an overall perception.

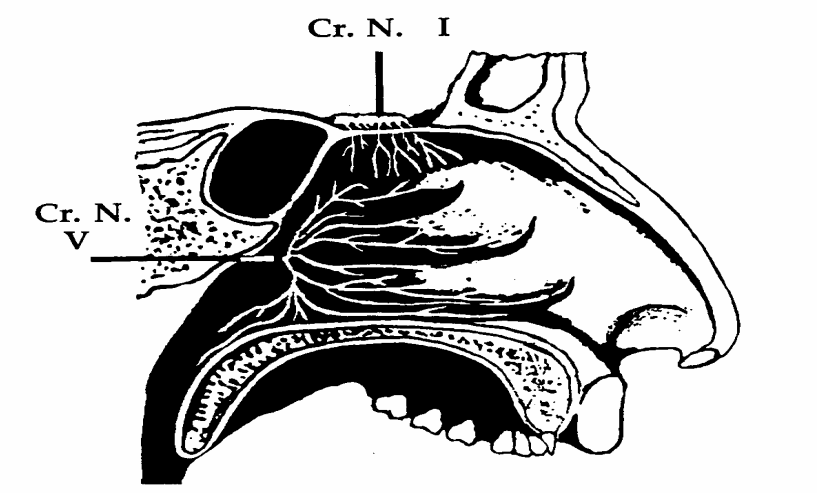

Figure 4 : Simplified anatomy and innervation of the lateral wall of the nasal cavity: Cr.N. I = first cranial (olfactory) nerve; Cr.N.V. = fifth cranial (trigeminal) nerve (Shusterman 1992).

For example, at low concentrations ammonia has a distinct odour; at higher concentrations however, the perception of ammonia is also characterised to be pungent, which is indicative for the irritation component of the overall perception. The lowest observed level at which a chemical exposure produces sensory irritation has been the basis for establishing exposure limits for a substantial number of compounds (Bos et al., 1992; Bos et al., 2002; Doty et al., 2004; Van Thriel et al., 2006).

When a volatile compound is inhaled into one nostril and air into the other, the stimulated side can be determined (lateralized) only after the concentration reaches a level that stimulates the trigeminal nerve; compounds (at concentrations) stimulating olfaction alone cannot be lateralized. The distinction between olfaction and chemesthesis allows to establish both olfactory and intranasal irritation thresholds.

Van Thriel et al.(2006) assessed odour and chemesthetic thresholds for 15 irritants, and found that these thresholds differed by a factor 10-10^6. For this study a static olfactometer was used which possibly biased the absolute values of the thresholds.
Odour and irritation sensitivity for methyl isobutyl ketone (MIBK, Dalton, 2000), glutaraldehyde (Cain et al., 2007) the plasticizer TXIB and ethanol (Cain et al., 2005) and ethyl acetate (Kleinbeck et al., 2008) were evaluated by obtaining olfactory detection and irritation (lateralization) thresholds, as well as perceived odour intensity and irritation ratings. The best predictors of perceived irritation to high concentrations of MIBK were those measures related to its odour, not to the threshold for sensory irritation. For glutaraldehyde, TXIB, ethanol and ethyl acetate odour detection also occurred at concentration levels well below levels resulting in chemesthesis, and this appears to be the general rule (Doty et al., 2004). This finding suggests that negative responses to these chemicals involve olfactory reactions, and that exposed individuals find olfaction difficult to distinguish from chemesthesis.

Individuals who lack a sense of smell (anosmics) can detect some, but not all, compounds through other chemosensory pathways although such compounds might produce a perceivable smell in normosmic subjects (Cometto-Muñiz et al., 2005b). This suggests that some compounds only stimulate the olfactory system, and not other pathways, such as the trigeminal nerve. Other compounds stimulate both pathways. These two chemosensory pathways to the brain may activate at different concentration ranges. For example, in anosmics the average *n*-butanol lateralization threshold was equivalent to the average *n*-butanol detection threshold. These thresholds for anosmics were equal to the average butanol lateralization threshold from normosmics, whose detection thresholds for *n*-butanol were substantially lower. This suggests that the detection of *n*-butanol in normosmics is driven by olfaction rather than by irritation (Kendal-Reed and Walker et al, 1996; Hummel et al., 1996).

However, several studies have suggested that anosmics may have lowered sensitivity to irritants, thus raising concern about the use of anosmic data to predict irritation thresholds for individuals with intact olfactory and trigeminal systems (Kendal-Reed and Walker et al., 1996; Hummel et al., 1996). Some studies suggest that anosmics have a lower trigeminal sensitivity than normosmics (Hummel et al., 2003) and that the processing of trigeminally mediated information is different in the presence or absence of an intact sense of smell, as determined with MRI imaging of the brain (Ianelli et al., 2006).

Wysocki assessed the sensitivity of olfaction and chemesthesis for acetone and *n*-butanol in workers habitually exposed to acetone in their working environment and in unexposed (naive)

subjects (Wysocki et al., 1997). The naive subjects experienced a different perception of irritation at concentrations of acetone that were below the intranasal irritation threshold. In general, the workers treated the stimuli simply as non irritating odours, whereas the unexposed subjects ascribed irritating qualities to the stimuli. The authors speculated about the possibility that concentrations of acetone and *n*-butanol that were well above the olfactory detection threshold but below the lateralization threshold could be annoying to some subjects, simply because they do not recognize the odour and attribute liabilities, for instance toxicity, to the compound.
Smeets and Dalton (2002) reported the same result for isopropanol, where the odour detection threshold was about 4 times higher in occupationally exposed individuals than in naïve subjects, and the irritation threshold a factor 2. Both thresholds were essentially equal for *n*-butanol; isopropanol exposed workers had a lower odour threshold (not statistically significant) for phenyl ethyl alcohol.

3.2 Somatic symptoms

The human response to perceived odour and irritant stimuli and their appraisal may be more driven by psychology than by the concentration of the odorants only. For example, in one experiment 90 adults were divided into three groups, each of which was given different information about chemicals to which they would be exposed (Dalton, 1997).

Table 2 : Selected Reported Health Symptoms in Subjects (n=30 for each group) after 20 min Exposure to 800 ppm Acetone compared. Adapted from Dalton (1997).

Symptom	Subjects exposed to odorant		
	Positive bias	Negative bias	Neutral
Throat irritation	4.36	8.69	8.59
Eye irritation	2.42	4.70	4.63
Nasal irritation	6.05	12.95	14.43
Lightheadedness	5.35	8.53	12.57
Headache	2.37	4.87	5.09
Nausea	1.9	2.60	5.17
Drowsiness	3.04	6.98	5.64

Researchers told the neutral group that the chemical they were to be exposed to is commonly used in olfactory research and approved for that purpose. The positive bias group was told that the odour was from natural extracts that are used in aroma therapy and that it is reported to have beneficial effects on mood and health. The negative bias group was told that the chemical was an industrial solvents that is reported to cause adverse health effects and cognitive problems following long-term exposure.

Following the exposure the subjects completed questionnaires to collect information on health symptoms. The positively biased group reported far fewer symptoms than the other two groups. Neutrally biased subjects responded similar to the negatively biased group. One interpretation for this finding may be that a normative response exists to unknown odours which is negative.
The overall pattern of results of this and other studies suggests that many of the health-related effects of exposure to odorants are mediated by cognitive variables, such as mental models of the relationship between environmental odours and health (Dalton, 1997). This hypothesis is supported by other publications and appears to be quite generic (Shusterman, 1992; Chen et al., 2005).

3.3 Annoyance

Investigations of the effects of odour exposure on health and well-being in the population have typically assessed annoyance as the main target (Steinheider, 1999). Annoyance is the complex of human reactions that occurs as a result of exposure to an ambient stressor that, once perceived, causes negative cognitive appraisal that requires a degree of coping (Van Harreveld, 2001).
Annoyance, related to noise, has been described in terms of three components (Clark, 1984):

1. an emotional component (for instance, a feeling of anger).
2. an interference component (for instance, disturbance of desired activities).
3. a somatic component (for instance, headache, nausea).

Since these three dimensions have been found to correlate rather well, simple one-dimensional annoyance scales have been used in field studies (Cavalini, 1991; Steinheider, 1999).
Whether or not one experiences odour as annoyance depends on perception and appraisal (Paustenbach and Gaffney, 2006). When a person detects a smell, a process of appraisal is started. If the odorant is associated with previous events in memory, and on that basis considered to be benign, it will not cause a negative cognitive response. On the other hand, when the odour is unknown, considered to be inappropriate in the behavioural context or appraised as harmful with possible health effects, annoyance is the likely result. Annoyance initiates coping behaviour, that may fall into two major categories:

1. Problem-oriented: attacking the problem caused by the stressor, for instance by closing windows to avoid malodorous air.
2. Emotion-oriented: regulating emotions caused by the stressor, for instance comforting cognition about health effects or ignoring its presence.

3.4 Nuisance

Nuisance is the cumulative effect on man, caused by repeated events of annoyance over an extended period of time, which leads to modified or altered behaviour (Van Harreveld, 2001). This behaviour can be active (for instance, registering complaints, closing windows, keeping ‘odour diaries’, avoiding use of the garden) or passive (only made visible by different behaviour in test situations, e.g. responding to questionnaires or different responses in interviews). Odour nuisance

can lead to infringement of our sense of well-being and cause increased levels of stress related symptoms which constitute a negative health effect. Nuisance occurs when people are affected by an odour they can perceive in their living environment (home, work environment, recreation environment) and:

1. the appraisal of the odour is negative,
2. the perception occurs repeatedly,
3. it is difficult to avoid perception of the odour,
4. the odour is considered a negative effect on their well-being.

Odour nuisance can develop after long-term intermittent exposure to odours that causes a negative appraisal in the individual concerned. It directly reflects with the way we value our environment (Van Harreveld, 2001). The development of nuisance is not a straightforward process. Our attitudes towards the source, the inevitability of the exposure, and the aesthetic expectations regarding our residential environment are some of the less tangible factors that are relevant to the probability of experiencing nuisance. Once the balance tips and an environmental stressor, such as a chemical or livestock odour, becomes a nuisance to an individual, it is very difficult to reverse the process and instil a positive connotation rather than a negative one.

4 Field considerations

4.1 Variation within the population

Olfactory responses of individuals vary with age. Increasing age is correlated with decreasing sensitivity, although the findings are not consistent. Furthermore, female panelists on average have a lower odour threshold than male panelists from the same age group. Factors such as health status (e.g., cold, nasal allergy), smoking behaviour, personality and training may contribute in some degree to the ability to assess an odour. The magnitude of the influence is shown in Table 3 as the ratio of the threshold in a subgroup as compared with an average healthy forty-year-old male (Amoore and Hautala, 1983).

Table 3 : Factors influencing the odour detection threshold (Amoore 1983).

Factor	Odour perception threshold versus average healthy forty year old male
Average woman	0.8
18 yr. male	0.5
62 yr. male	2
Smoking during test	4
Chewing during test	4
Head cold	4
Nasal allergy	4
Undirected test	4

Average 40-year old male = 1.

Van Thriel et al., (2007) reported age related differences in odour thresholds for 3 out of 15 irritant chemicals in two groups with mean ages of about 25 and 54 years, odour thresholds in the > 45 year group were about twice those of the young adult group. Boesveldt however (2008) reported a decrease in odour discrimination scores as determined with 'Sniffin' Sticks' (16 odours) among women, but not men in 150 subjects aged 47-78 years. Stevenson et al., (2007) found that 6-year old children performed less well than young adults in a series of odour discrimination tests. This was likely due to a lesser olfactory discriminative ability, and not (completely) due to their inability to describe names of odours.

Katotomichelakis et al., (2007) found that the odour threshold as determined with 'Sniffin' Sticks' was 4 times higher in smokers (not smoking during the test) compared with non-smokers. Odour discrimination (the ability to identify which of 3 presented odours differed from the other two)

was reduced 5-fold in the smokers. In addition a decline in odour threshold and discrimination was found with age.

Subjects in good health can normally reproduce their individual odour thresholds for a certain compound within a factor ±2. Intra-individual variation is relatively small compared to inter-individual variation. Dutch data on inter-individual variation are available for over 1000 individuals who answered to panel recruitment for odour perception studies (Van Harreveld et al., 1999). The variation in odour thresholds in this group is large, with a difference of approximately a factor 30 between the top and bottom 5% of the distribution, corresponding to a standard deviation of 3.2. This group is not a proper random sample of the population, and the inter-individual variation in the general population is likely to be larger.
Other sources state that the standard deviation in the distribution of individual odour thresholds is approximately the same for all tested odorants, averaging very close to a factor of 4 (Amoore and Hautala, 1983). In practice this means that two-third of the general population will be able to detect concentrations between 1/4 and 4 times the odour threshold. Less than 2% (hyperosmic or hypersensitives) are able to detect a concentration 10 times below the ODT and less than 2% (hyposmics including anosmics) are unable to detect a concentration of 10 times the ODT (Figure 5).

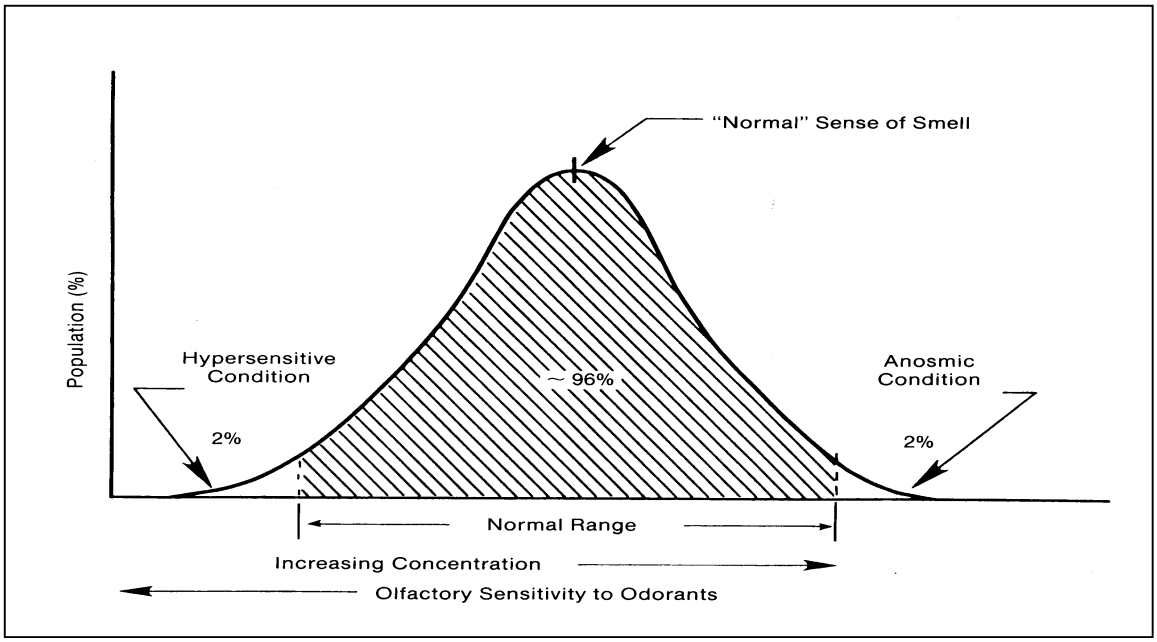

Figure 5 : The sensitivity in the sense of smell within a population (AIHA 1989).

4.2 Distraction and adaptation

There is a substantial difference between the level of odorant that *can* be detected, and the level that *will* be detected (Whisman et al., 1977). In a study on the influence of various degrees of distraction on the responsiveness of people to well-known warning odours, substantial differences

where found between directed and undirected tests. In a *directed test*, the attention of the subject is purposely focused on the sole objective of detecting odour. In the *undirected test*, the subjects were given no indication of the object of the exercise. Recalculation of the data on log/probit coordinates resulted in a four-fold increased detection threshold for the undirected test as compared to the directed test (Amoore, 1985).

With continuing exposure to a certain odour concentration, the sensation gradually decreases, and may even disappear. Olfactory fatigue from continued exposure to an odour may affect a person's sense of smell. This phenomenon is called adaptation (US EPA, 1992; Shusterman, 1992). Adaptation begins to reduce perceived odour intensity and quality during the first inhalation. Adaptation may reduce both perceived odour intensity and perceived odour quality. The degree of adaptation resulting from exposure to an odorous air will depend on the odour concentration experienced. The weaker the odour concentration of an air sample, the more does adaptation affect perceived strength. Although adaptation takes some time to develop, recovery takes place more quickly. Recovery periods may range from seconds to minutes depending upon type and concentration of odour and duration of exposure. It has been pointed out that while sensitivity to an odour may decrease after sniffing a sample, 80 to 90% recovery generally occurs within a minute with complete recovery in several minutes (Shusterman, 1992, EN13725:2003).

During exposure to hydrogen sulphide, most subjects experienced an exponential decrease of intensity, that dropped to a steady level within 2-5 minutes, and did not change appreciably up to 15 minutes later (Ekman et al., 1967). One of eight subjects indicated virtually complete loss of odour sensation and another a substantial loss which is attributed to reversible paralysis of the olfactory nerve. The other six showed an approximately 50% decrease of perceived intensity, which corresponds to an apparent four-fold reduction in the hydrogen sulphide concentration. After breathing pure air, the sensitivity recovered almost completely in about four minutes.

In most situations a mixture of odorants, rather than just a single compound, will cause odour detection. One single compound may excite more than one type of olfactory receptor, while a different odorant is likely to excite a different subset of the 350 types of human olfactory receptor cells. Studies have been undertaken on the perceived intensity of odour mixtures by mixing two odorants, both above the detection threshold. The typical finding was that the perceived intensity of a mixture is less than the arithmetic sum (hypo-addition) of the individual intensities (Berglund et al., 1973; Cometto-Muñiz et al., 2005a).

4.3 Peak to mean ratio in odour exposure

Field conditions typically apply to chemical emergencies, where the odorant concentration will vary significantly due to atmospheric turbulent dispersion. The population is typically exposed at a

few hundred to a few thousand meters distance from a (point) source, and their sense of smell will assess the atmosphere with every breath.
The perception of odours is very quick. One breath inhalation takes approximately 3 seconds. One inhalation can lead to odour detection, perception, and appraisal. As we spend approximately half of our time exhaling, a practical value for the smallest period of interest to assessing the effects of odours is therefore approximately 5 seconds. No matter the duration of the exposure to an odorant, it is known that the peaks (not the average concentration), the height of peaks and the frequency of occurrence of peaks are important in determining the perception of the odour (NSW EPA, 2001). Therefore, peak to mean ratio caused by turbulent atmospheric dispersion on a 5 second time frame scale will be relevant, with the peaks determining the awareness of the presence of an odour. At the edges of the zone of distinct odour awareness the variations will cause alternating periods of low exposure with peaks in concentration. These peaks are determining the appraisal by the exposed population. In the long run, adaptation or habituation may reduce the perceived odour intensity (Shusterman, 1992), although in typical field conditions the short time required for recovery from adaptation implies that this phenomenon will not be a major factor in assessment and appraisal by the public.

Given the rapidity and reversibility of the odour response, the usual time scaling of AEGL and ERPG values seems inappropriate for the odour endpoint. Dispersion modelling typically produces 10-60 minute to exposure level averages, while for acute odour responses, a timescale of 5 seconds is appropriate. Therefore it makes sense to adjust for the peak-to-mean ratio of the variable concentration level. In a proposed odour guideline for New South Wales, Australia, factors were recommended for estimating peak-to-mean concentration ratios for different source types, stabilities and distances (NSW EPA, 2001). These factors are applied in screening procedures for flat terrain situations. At distances of more than 200-1000 meters peak to mean ratios were 1.9 to 7. Based on the current state of the art, a default value of 3 is considered to be the best estimate for adjusting exposure levels averaged over 10-60 minutes, which are relevant in emergency response planning, to 5second peak exposures that are determining for acute odour perception in the field. This means that on any proposed odour criterion a factor 3 has to be applied to typical 10-60 minute averaged concentration levels predicted by dispersion modelling to account for peak concentrations of 5 second duration within that 10-60 minutes of exposure.

5 Significant odour awareness

Any unusual odour not common to the normal 'odour landscape' has the potential to cause arousal and awareness of a smell in individuals. The probability that this happens increases with odour concentration. Consensus was reached in the AEGL program that a concentration where more than half of an accidentally exposed, distracted population perceives a distinct odour would qualify as significant odour awareness. This concentration is designated as 'Level of distinct Odour Awareness (LOA)'.
For some people exposure to the odorant may go unnoticed, especially in areas where a certain odour landscape is already present. In densely populated areas however, the probability that more than a few persons will react to the exposure will increase and can become significant. Health and environmental authorities will get involved because of public information requests.
A stepwise procedure to derive the LOA for a chemical is introduced below. The general idea behind the procedure is to apply currently available knowledge and data to make a best estimate wherever robust specific knowledge or data are lacking. As with other AEGL endpoints for derivation of toxicologically based guideline levels, the knowledge of the underlying mechanism and the quality of the data is rarely adequate. Some defaults have been developed to circumvent incomplete knowledge and data (much like time scaling for toxic endpoints).

The stepwise procedure to provide a LOA for a certain chemical, is provided in the following paragraphs.

5.1 Obtain the odour detection threshold (ODT)

The first step is to obtain a reliable population odour detection threshold (ODT) for the compound. Modern standards for forced choice dynamic olfactometry, which require traceability to reference odorants and adherence to minimum performance criteria, have greatly improved the sensitivity, repeatability and reproducibility of odour measurement. Unfortunately, the availability of ODT data for pure compounds, as determined according to EN13725:2003 or equivalent standards, is limited. So far, no authoritative compilation of such ODTs has been located. To avoid that this lack of data hampers the application of odour characteristics to a wide range of compounds, the following three tiered classification of odour threshold data quality is proposed:

Level 1: *the ODT of a compound determined according to EN13725:2003, AS/NZS4323.3:2001, NVN2820 (or equivalent) or the 'Triangle Odor Bag Method'.* Because these standards require minimum performance criteria, it is possible to determine a geometric mean value from the data of one or more laboratories if necessary after adjustment for the *n*-butanol ODT. Additionally it is possible to derive the uncertainty of this mean value, based on the number of available test results, and the

stated uncertainty for the laboratories involved. Some laboratories may work under international accreditation to quality assurance standards such as ISO17025 or data may become available from inter-laboratory comparisons related to such accreditation. That type of independently verified data constitutes the most reliable source.

Level 2: *ODT from a source that includes a reported value for n-butanol.*
If no level 1 ODT is available, an attempt can be made to derive a level 2 ODT. If internal consistency of results (long term repeatability) can be established for a laboratory, or if a compound with a known reference compound for which a Level 1 quality value is available was analysed in one measurement session, using the same panel of assessors, a correction can be made for the sensitivity of the method in question relative to a traceable method. The ratio of the experimental threshold, for instance for *n*-butanol determined in a test panel and the reference value of 40 ppb can be used to calculate a level 2 ODT.
For example: the ODT for styrene in a test panel was 30 ppb. In the same panel the ODT for *n*-butanol was assessed as 100 ppb. In this case the level 2 ODT for styrene is estimated to be 30 x 40/100 = 12 ppb.
If two or more level 2 ODTs can be calculated the applicability and quality of the available sources can be evaluated, and a geometric mean value of all qualifying sources can be used as a point of departure for calculating the LOA
Nota bene: this procedure requires ODT data for *n*-butanol and the odorant from one primary literature source. Listing in an odour review will not suffice, because the presented ODTs may have been determined in many different laboratories.
Once level 1 ODT values become available for a wider range of chemicals, the adjustment could also be performed with chemicals other than *n*-butanol with a level 1 ODT.

Level 3: *ODT without an internal reference to an n-butanol or level 1 ODT.*
If no level 1 or 2 ODTs can be calculated, a level 3 ODT can be used. Such ODTs are often found in compilations such as by AIHA (1989) and US EPA (1992). These compilations critique thresholds reported in literature based on:

1. The quality of the reference (secondary source, incidental reference, passive exposure, availability).
2. The odour panel: panel size, panel member selection and calibration.
3. The presentation apparatus: vapour modality (gas/air mixture or vapour over aqueous solution), diluents, presentation mode, analytic measurement of concentrations and system calibration (including presentation flow)
4. The presentation method: threshold type, concentration presentation (includes duration), number of trials, forced choice method and the concentration steps used.

The main issues that cause limited applicability of odour studies are too low stimulus presentation flow (< 10 liter/minute) and lack of a reference odour in the panel session to ascertain panel sensitivity.

In these cases, the crude but most effective approach is to use the lowest reported value from all acceptable sources (Code A for AIHA and US EPA 1992). The geometric mean would be misleading, because the bias introduced by inadequate testing methodology is almost without exception towards higher odour thresholds.

The choice or determination of a level 1 or 2 ODT requires review of the primary literature source, as is customary when deriving toxicologically based guideline values. At the least a common primary source for the 2 chemicals used in the calculation of a level 2 ODT should be verified. Generation of new olfactory data of quality level 1, preferably by accredited laboratories, is an option when data are absent or insufficient.

Odour reviews can be very valuable resources for identification of ODT data. Large listings can be found in Nagata (2003, level 1), Van Gemert (2003), AIHA (1989), US EPA (1992), Van Thriel et al., (2006), Cometto-Muñiz and Abraham (2008), Katz (1930), Helman and Small (1974) and Punter (1983).

5.2 Derive distinct odour level

In odour laboratories odorant concentrations leading to distinct odour detection can be estimated. An alternative is to use the Fechner function (cf. section 2.2), preferably using an experimentally determined value of k_w for the compound in question:

$$I = k_w \times \log (C/\mathrm{ODT}) + 0.5$$

Experimentally derived k_w values are available for a limited number of chemicals. Sources with information on odour intensity include VDI (1992) and Cometto-Muñiz et al. (2005).
Some sources provide odour intensity information as Steven's coefficients (Patte et al., 1975). These can be used as an alternative way to calculate a distinct odour level, even though the methodology has not been standardized and the conversion is by no means straightforward.

The range of experimental k_w values is surprisingly small with a median value of 2.33. If no experimental k_w value is available, it is suggested to use the median value of 2.33 as default. When the default is used, the intensity perceived by 50% of a population exposed to an odorant concentration C is predicted by:

$$I = 2.33 \times \log (C/\mathrm{ODT}) + 0.5$$

Concentrations corresponding to various perceived intensities can now be calculated. The concentration that is expected to lead to perception of a distinct odour (I=3) equals 11.8 × ODT. This means that 12 odour units per m^3 can be expected to generate distinct odour perception under laboratory conditions.

5.3 Adjust for field conditions

Outside of the laboratory, factors such as sex, age, sleep, smoking, head cold and nasal allergy influence the perception of odours. Distraction (the fact that in a laboratory the individual's attention is purposely focused on detecting odours, whereas this in not the case in ordinary life situations) increases the operational ODT by a factor of 4 (Amoore, 1985).

The perception of odours is very quick. One breath with a total duration (inhalation and exhalation) of approximately 5 seconds can lead to odour detection, perception and appraisal. For such rapid effects, the average concentration over a certain time period does not predict the response very well and the usual methodology for time-weighting of effects is not applicable. We clearly need to account for peaks in the exposure pattern, where we are interested in the frequency of peaks that exceed the detection threshold criterion. To account for the peaks, various 'peak-to-mean' ratios have been proposed and applied in odour control policy. To convert on-hour average concentrations predicted by dispersion modeling to reflect 5 second peak values, lowering the 1-hour average concentration by a factor 3 is considered to be the best estimate (NSW EPA, 2001). Accounting for the peak-to-mean ratio is the most appropriate way to time-scale AEGL-values for the odour endpoint.

Adjustment for distraction and peak exposure leads to a combined correction factor of $4 / 3 = 1.33$ from laboratory to time-weighted average field conditions. It follows that we expect that 16 odour units/m^3 (or 16 × ODT under laboratory conditions) will lead to a distinct odour perception among a significant proportion of members of the general population under field conditions.

6 Conclusions and recommendations

6.1 Conclusions

Detectable odour concentrations can generate anxiety in a relevant proportion of members of an exposed community are not necessarily toxicologically significant levels. Rather they represent concentrations where notification (i.e., informing the public about properties of the unusual odour) is recommended to modulate appraisal of odour with the aim of reducing or preventing the incidence of anxiety and associated stress-related health effects.

This paper presents criteria for a 'Level of distinct Odour Awareness' (LOA) in accidental exposure of the general population. Despite many knowledge and data gaps, a methodology for which sufficient agreement exists has been developed. The method has been applied to a number of AEGL chemicals, and the approach delivers a LOA value that can be applied in practice.

The methodology needs to be validated much more rigorously, and this document and the methodology described should be regarded as a first step towards development of a practically useful metric. Adequate validation requires additional information that is currently insufficiently available.

6.2 Recommendations

The LOA can only be determined on a chemical-by-chemical basis. Many of the data required to do so for chemicals relevant for emergency planning and response are lacking or of poor quality. The procedure outlined in chapter 5 produces the best available quantitative assessment of a LOA. It is recommended that an attempt is made to develop a LOA for each chemical under review for development of acute guideline values (AEGL, ERPG, Dutch Intervention values, and others).

The validity of the derived LOA values would be greatly enhanced if the following knowledge and data would be available:

1. High quality assessments of the concentration leading to distinct odour perception under laboratory conditions for relevant chemicals, or alternatively:
   - Well determined (level 1) odour detection thresholds, and
   - Fechner coefficients
2. Information about necessary adjustments for field conditions such as colds, attention, smoking and variability of the exposure level to derive a LOA based on the distinct odour level from the laboratory.

All this information should be available in the public domain or for the specific purpose of development of LOA values.

To validate the approach, systematic observations of odour annoyance should be made in chemical emergencies. The methodology to make such observations should be developed or adapted from existing methodologies. The methodology to derive LOA values should be adjusted accordingly. The possibility for experimental validation should also be explored.

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Appendix 1: The olfactory system

In olfactory sensory systems, peripheral neurons receive information from the environment and transmit this information to the brain, where it is processed. The olfactory system is intimately involved with limbic system function, and odours have a powerful ability to elicit stirring emotions and memories of past events. Olfactory neurons actually physically link our brain to the environment, and thus represent the most direct interface between the brain and the external world. When a chemical excites a neuron, the signal is transferred to the olfactory bulb. This structure, located in the very front of the brain, is the clearinghouse for the sense of smell. From the olfactory bulb, odour signals are relayed to both the brain's higher cortex, which handles conscious thought processes, and to the limbic system, which generates emotional feelings. In the brain, nervous signals coming from olfactory cells are linked to signals from other sensory input information.

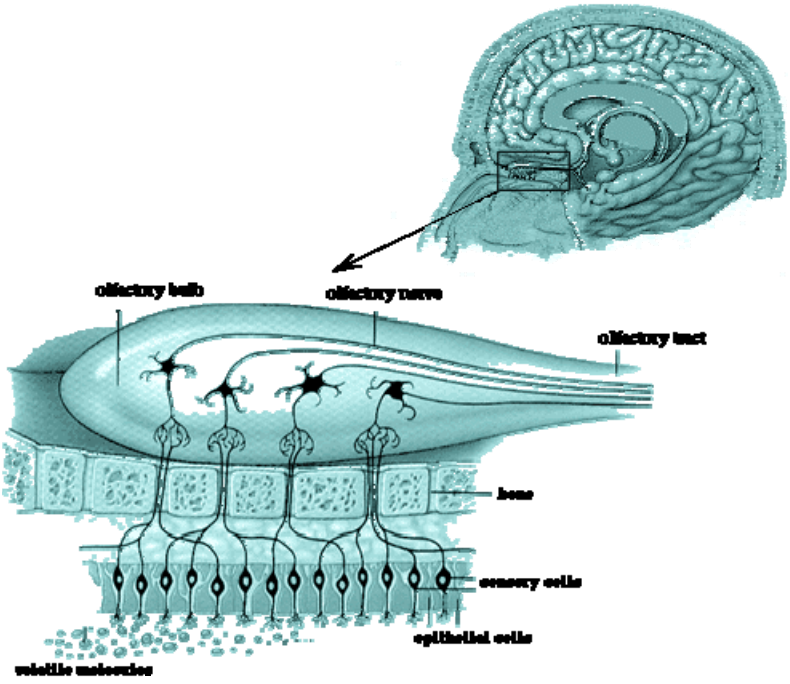

Figure 6. The physiology of odour perception.

Source: http://www.sciencenet.org.uk/database/Social/Senses/s00122b.html

Odour as perceived in the brain may be a response based on a range of different olfactory receptor stimuli experienced as sensations in the individual's olfactory system. The olfactory region of the nasal *mucosa* is located in the cribiform plate of the ethmoidal bone and comprises an area of about 5 cm^2, containing in total approximately 50 million primary sensor receptor cells (Leffingwell, 2000). The olfactory region consists of cilia projecting from the olfactory epithelium into a layer of mucous (Figure 6). This mucous layer is a lipid-rich secretion that bathes the surface of the receptors at the epithelium surface. The mucous lipids assist in transporting the odorant molecules because only materials that are soluble in the mucous can interact with the olfactory receptors to produce the signals that our brains interpret as odour. Each olfactory receptor neuron has 8-20 cilia that are whip-like extensions 30-200 micrometers in length. The olfactory cilia are the sites where molecular binding of the odorant occurs and sensory transduction starts. Above the mucous layer is the base olfactory epithelium which consists partially of basal cells which are capable of mitotic cell division to form olfactory receptor neurons when functionally mature. The olfactory receptor neurons turnover approximately every 40 days. Sensory neurons extend a single unbranched axon to the olfactory bulb in the brain such that the projections from neurons expressing a specific receptor converge upon discrete loci called *glomeruli*, which then converge onto mitral cells. Each of the 350 types of olfactory receptor cells connects to a specific glomerulus for that type. The olfactory bulb provides spatial maps that identify which of the numerous receptors have been activated within the sensory epithelium.
The olfactory receptor sites are on the ciliary surface membrane. Odorant stimuli bind to a protein receptor site in the membrane. The stimulus activates G-proteins which evoke an enzyme cascade. At the end channel proteins are phosphorylated that may affect gating of ion channels (Figure 7).

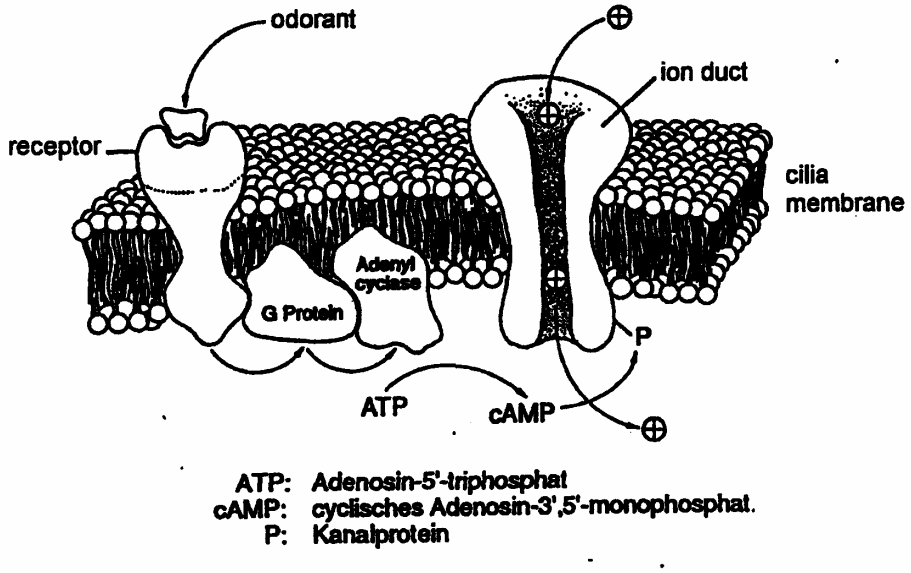

Figure A2 Model of olfactory membrane and transmission of signals. Modified from Plattig, H.H. Spümasen und Feinschmecker. Die Chemische Sinne des Menschen., Berlin, Heidelberg, New York, Springer Verlag,1995.

Figure 7. Model of olfactory membrane and transmission of signals. (Plattig, 1995)

In 1991, Linda Buck and Richard Axel discovered both the family of transmembrane proteins that are believed to be the odour receptors and some of the genes that encode them (Buck, 1991). They cloned and characterized different members of an extremely large multigene family that encodes the seven transmembrane proteins whose expression is restricted to the olfactory epithelium. This was a breakthrough in our understanding of the olfactory system. It is now estimated that there are 350 odorant receptor genes in humans. This number of genes, specific to the olfactory system, comprises 1% of the approximately 30,000 functional genes thought to make up the human genome. This number is second only to the receptors of the immune system. The enormous amount of genetic information devoted to smell perhaps reflects the evolutionary significance of this sensory system for the survival of most mammalian species (Axel, 1995).

It appears that the sense of smell in mammals is based on a combined approach to recognizing and processing odours. Instead of dedicating an individual odour receptor to a specific odour, the olfactory system uses an ‘alphabet’ of receptors to create a specific smell response within the neurons of the brain. As in language, the olfactory system appears to use combinations of receptors to reduce the number of receptor types required to convey a broad range of odours. Thus, 350 or so receptors in humans can detect many thousands of distinct chemicals (Buck, 2005).

Slight changes in chemical structure activate different combinations of receptors. For example octanol smells like oranges, but the structurally similar compound octanoic acid smells like sweat, based on the receptors activated (Buck, 2005). It was found that large amounts of a chemical bind to a wider variety of receptors than do small amounts of the same chemical. This may explain why a large whiff of the chemical indole smells putrid, while a trace of the same chemical smells flowery.

Appendix 2: Olfactometry

Because there are no instrumental methods that predict the responses of our sense of smell to a satisfactory degree, the human nose is the most suitable 'sensor'. Olfactometry employs a panel of human noses as sensors. In one of the modern olfactometry testing procedures (EN13725:2003), a diluted odorous mixture and an odour-free gas (as a reference) are presented separately from two sniffing ports at 20 ℓ/min to a group of at least four panelists. In comparing the gases emitted from each port, the panelists are asked to report the presence of odour together with a confidence level such as guessing, inkling, or certainty. The gas diluting ratio is then decreased by a factor of two (chemical concentration is increased by a factor of two). The panelists are asked to repeat their judgment. This continues for five or six different dilution levels, resulting in a total of almost hundred judgments from at least four panelists. The panelists can also be asked to give information about perceived intensity and perceived pleasantness of the odour sensation.

Odour detection thresholds

Detectability is the most common attribute used to characterize odours. Detectability refers to the minimum concentration of odorant necessary for detection by some specified percentage of the test population. In chemosensory detection, other pathways may contribute, such as the trigeminal nerve (irritation) and the vomeronasal organ. Using panelist responses over a range of concentrations, the odour threshold concentration can be assessed. The variability and likelihood of detection both within and between individuals plays a role:

1. As with any psychophysiological measurement (odour, hearing, sight, vibration, etc.), the likelihood of an individual to detect a signal is related to the stimulus intensity. In this case, the likelihood that an individual will distinguish the chemical stimulus from odour free neutral gas is related to its airborne concentration. An individual's odour threshold is usually defined as the concentration where this likelihood is 50% (cf. Left part of figure 2, Cometto-Muñiz and Abraham, 2008).
2. The population odour threshold is the airborne concentration at which 50% of the population can smell the odorant. This odour threshold is usually determined by a limited number of panelists in an olfactometry experiment (cf. right part of Figure 8). At the odour detection threshold (ODT), the odour concentration of an odour sample (single compound or mixture) is defined to be 1 odour unit per cubic meter. In modern olfactometry standards (EN13725:2003, AS/NZS4323.3:2001) the odour unit is linked to a specific concentration of a reference odorant, such as 1 ou_E/m^3 (European Odour Unit) ≡ 40 ppb/v *n*-butanol. In a preceding Dutch standard the reference level was different, at 20 ppb/v *n*-butanol, which leads to a conversion factor of 2. Olfactometry before 1996 was not linked to a mass of a reference odorant as a standard stimulus, and therefore are not defined as a unit. The relation to the defined mass unit of a reference odorant is implemented by selecting a sample of qualified panel members from the population of assessors with olfactory sensitivity close to that agreed reference value.

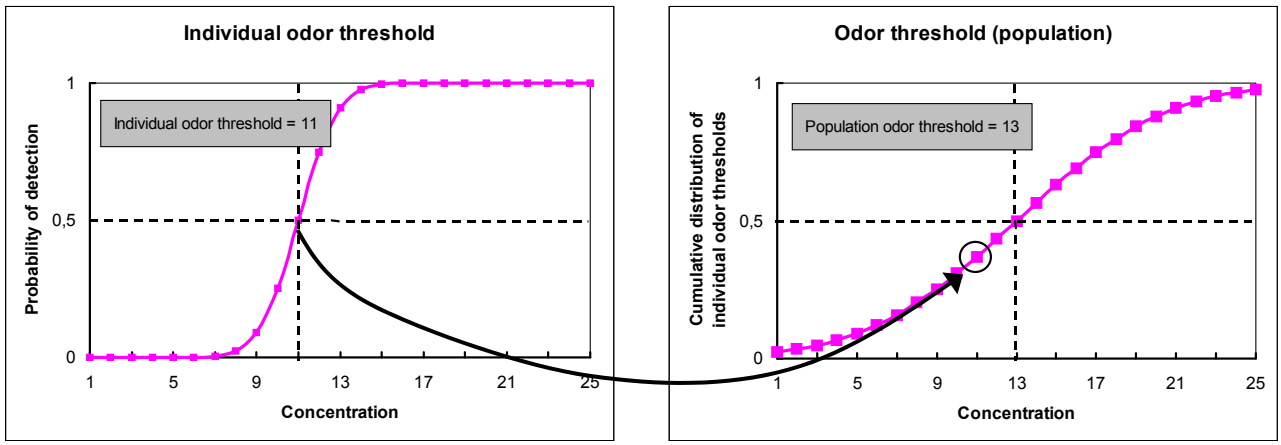

Figure 8: Individual and group odour detection thresholds.

The way in which the response of our sense of smell is reduced to a single value of a parameter amounts to a gross simplification of the rich spectrum of sensory information that is actually perceived by the brain. Such a simplification may be useful, however, in describing potential effects. The reduction of a very complex physiological process to a simple parameter is methodologically very similar to expressing the effects of toxic substances on an organism as the LC_{50}, which indicates the concentration causing lethality in 50% of a well-defined test population. The complex physiological response is regarded as the unifying reaction that can be caused by a wide range of substances, at an equally wide range of concentrations.

In general terms, this approach can be used to describe the potential of a certain amount of a substance to cause a physiological effect, by expressing the dose as a multiple of the dose that would cause an effect in 50% of a population. The definition and use of the unit are highly analogous to that of the odour unit. In odour research, the ODT could be described as the concentration at which 50% of a population detect a sensory stimulus. Odour detection thresholds were reported for a large number of compounds. There are a few compilations available. Unfortunately most reported odour thresholds were obtained using old methodology which did not take into account significant operational variables, that were identified accurately by Dravnieks (1980). The main factors identified have later been confirmed to be the main issues in improving reproducibility (Van Harreveld, 1998).

The main issues are:

1. **Standardisation of stimulus flow rate at presentation**
   At lower flow rates below peak inhalation rate during sniffing, environmental air will be

inhaled and cause extra dilution. This effect has been quantified by Dravieks and Jarke (1980), Dupraz (1990) and O'Brien et al. (1996). The stimulus presentation flow rate is standardised at 20 ℓ/min or more in NVN2820, EN13725 and AS/NZS4323.3:2001. In the USA this is an issue under discussion, with some instruments converging to EN13725:2003 requirements, and others operating at flow rates as low as 0.5 ℓ/min.

2. **Panel selection**
   The main issue that has caused convergence of odour detection threshold results for different laboratories is selection of assessors using a reference odour, in a defined range around an agreed consensus value. EN13725:2003 uses *n*-butanol, at a target value of 40 ppb/v, equivalent to 1 ou_E/m^3 (Van Harreveld et al., 1998). Other standards that have included such traceability are NVN2820 (reference value 20 ppb/v = 1 ge/m^3, ge = Dutch odour unit). Many other standards (VDI3881, ASTM standards etcetera, etcetera) have less rigorous traceability and result in odour units that are not traceable to a defined mass unit.

3. **Calculation method**
   EN13725:2003 provides a detailed statistical procedure to calculate the ODT and other parameters from the data. Other statistical procedures may produce slightly different values.

In the past odour researchers have not used populations of standard test subjects, and have only related the physiological response to the number of dilutions of the dose of a sample to be measured. That practice implies a fundamental inability to compare the dosage of the samples through other means than the population itself.
This can only be justified if the researcher is convinced that the samples of the population are sufficiently large to compensate for biological variability within this population. This assumption, however, cannot be fulfilled in the practice of odour measurement. The small sample from the population (typically 4-8 subjects, more or less randomly chosen) is far too limited a sample to be representative, knowing the variability of sensitivity within the population. This practice does not comply with statistical requirements as used in toxicological experimental design, as the sample size from the population required to be representative (hundreds) is far greater than the regular number of panel members used in olfactometry for environmental applications.

The solution is to standardize the test subjects used to assess the sensory response without introducing a bias. Reproducible results can be obtained by selecting panel members with a known sensitivity to an accepted reference material (currently *n*-butanol). The assumption is that the sensitivity for the reference odorant will predict the sensitivity to other substances. The dose of other substances and mixtures is then expressed in multiples of the dose that would elicit a physiological reaction equivalent to that of the reference.

Standardizing odour thresholds in this way presumes that an individual's sensitivity to *n*-butanol will predict their sensitivity to all other odours. However, just as olfactory sensitivity can vary widely across a population to the same chemical, olfactory sensitivity to different chemical compounds can vary dramatically within the same individual. In other words, because olfactory

sensitivity at any given point in time is determined by both genetic and environmental factors, there is no a priori way to predict that sensitivity to a single chemical can act as a surrogate for sensitivity to all chemicals. It is likely that everyone is relatively insensitive to certain chemical molecules. Nonetheless, is the use of at least one internal standard an important step forward compared to not using a referent compound at all. It is very encouraging that there is such an excellent agreement between Dutch and Japanese studies (Appendix 3). For approximately 20 compounds the difference in reported standardized odour thresholds is well within a factor 2.

Accuracy and precision criteria in threshold detection

Olfactometry requires a very high standard of testing conditions. These include an odour-free testing environment, a highly accurate and repeatable olfactometer and effective panelist management. Since the early 1990s, the introduction of improved instrument calibration, improved panel screening procedures and the adoption of *n*-butanol as a reference material, have enabled more objective odour concentration measurement (Van Harreveld et al., 1998).

The performance of an odour laboratory can now be assessed in terms of measurement accuracy in relation to an agreed reference material such as *n*-butanol. Two terms, 'accuracy' and 'precision' describe the 'trueness' of a measurement method. Accuracy (absence of bias) is defined as the closeness of agreement between the average test result of a method and an accepted reference value and may be investigated by comparing an accepted reference value with the level of the results given by the measurement method. Precision (repeatability and reproducibility) involves the random errors inherent in every measurement procedure. Precision describes how close repeated measurements are to each other. While the term 'repeatability' is used to describe precision in the same laboratory, the term 'reproducibility' is used to describe precision of a method as attained between laboratories.

Currently, the preferred and internationally standardized methods of measuring odour is the European CEN standard EN13725:2003, which was in part inspired by the earlier and now obsolete Dutch preliminary standard NVN2820:1994.. The performance of odour concentration measurements has been defined in the performance criteria of the standard.
At standard conditions for olfactometry, the reference value corresponds to an *n*-butanol concentration of 40 ppb (Note: for the NVN2820 standard the reference level was 20 ppb *n*-butanol). The overall sensory quality criteria are:

- bias equal to or less than 0.217. Each separate determination of an *n*-butanol odour threshold should fall within a factor of $10^{0.217}$, corresponding to 24-66 ppb
- repeatability not greater than 0.477. This means that only results of laboratories are accepted that are able to reproduce the odour threshold of *n*-butanol within a factor $10^{0.477}$ in 95% of cases, corresponding to 13-120 ppb.

Eighteen European countries have been able to agree on an olfactometry standard in a relatively short time. An inter-laboratory comparison study of olfactometry in Europe was undertaken in 1996. The study demonstrated that individual laboratories following the methods specified in the

draft CEN standard for odour concentration measurement can achieve quality requirements as specified in the standard (Van Harreveld 1998).

Modern performance based forced choice dynamic olfactometry has greatly improved the sensitivity, repeatability and reproducibility of odour measurement. For instance, the butanol threshold measured using a three port IITRI olfactometer ranged from 80 - 200 ppb, while modern dynamic olfactometry is capable of measuring butanol threshold levels in the range of 20 to 80 ppb. Correspondingly, a threshold of 1 odour unit per m^3 determined with the less sensitive earlier methodology could be rated 2 - 5 odour units per m^3 using modern equipment. Appendix 3 presents an overview of standardized odour thresholds.

Appendix 3: Consistency of odour thresholds

There are a number of odour threshold compilations available (Amoore and Hautala, 1983; Ruth, 1986; AIHA, 1989; US EPA, 1992; Van Gemert, 2003). Odour thresholds reported before 2006 probably were not obtained under the same conditions of methodological precision that are taken for granted today, and are not traceable to a defined mass unit. Additionally some values are reported from many interdisciplinary sources in which the intent is not threshold measurement per se. The lack of standardization of methods for odour threshold determination, taken in conjunction with inconsistent purity of chemical samples and the variability of human sensitivity, is esponsible for the wide range of threshold concentrations usually found in the literature for a given compound. For example, 26 values were reported for hydrogen sulphide, ranging from 0.072 - 1400 ppb, that is a factor 10.000 (Amoore, 1985).

An AIHA Review Subcommittee presented a critique of the experimental odour thresholds reported in the literature (AIHA, 1989). They considered this a necessary refinement for obtaining best estimates of odour thresholds. A two-phase review was conducted of 366 references from two odour threshold compilations. The review was limited to chemicals with published occupational threshold limit values. Ninety percent of the references were rejected, based on review (e.g. secondary source, incidental reference) or criteria for acceptability (sufficient panel size, actual analytical measurement of odorants, calibration procedure). A similar approach was followed in the more recent compilation by the U.S. EPA (USE92).
The table on the next page shows a collection of data, comparing results of odour thresholds for compounds in ppm. The following methods are compared:

- Methods of olfactometry considered compatible with a precursor of the NVN2820 and EN 13725 methods
- Measured by TNO in the Netherlands, 1988, using a precursor of the NVN2820 and EN 13725 methods, with a mean *n*-butanol threshold of 25 ppb. Results of A and B have been converted to the reference value agreed in EN13725 of 40 ppb *n*-butanol by applying a correction factor of 40/25 = 1.6
- The Japanese triangle olfactometer method. The method uses panel selection based on screening of assessors using reference odours and produces an an-butanol threshold of 38 ppb/v, which is compatible with EN13725 (Hoshika et al., 1993; Nagata, 2003).

The results are very clearly supportive of the benefit that can be obtained by standardization and use of reference odours for quality assurance. The differences between the methods are quite small compared to those commonly reported for olfactometry. Only for ammonia the differences are two orders of magnitude. Ammonia is mainly an irritant and therefore not all that relevant for comparisons of odour thresholds.

	Odour threshold, mean of ABC	NVN2820 compatible (A)	TNO 1988 (B)	Japan, C	Factor of difference		
					B/A	C/A	C/B
Styrene (vinylbenzeen)	0.0345	0.049	0.025	0.033	0.51	0.67	1.32
Butyric acid	0.000086	0.00011		0.00007		0.64	
4-methylpentanon-2	0.144	0.123		0.170		1.39	
m-xylene (1,3, dimethylbenzene)	0.19	0.18	0.20		1.09		
Toluene (methylbenzene)	1.27	1.39	1.59	0.92	1.14	0.66	0.58
Phenol	0.017	0.018	0.016		0.89		
Pentanal (valeraldehyde)	0.0007	0.0008		0.0007		0.93	
Propanal (propionaldehyde)	0.0016	0.0017		0.0015		0.88	
butanal (butyraldehyde)	0.00031	0.00031		0.00031		0.99	
Tetrachlooretheen	2.28	2.67	1.95		0.73		
Ethyl acetate	0.26	0.27		0.25		0.91	
Isovaleric acid	0.00005	0.00006		0.00005		0.97	
Dimethyldisulphide	0.00035	0.00043		0.00028		0.67	
n-butanol	0.039		0.040	0.038			0.95
Methanethiol (methylmercaptan)	0.00012	0.00014		0.00010		0.74	
Dimethylsulphide	0.00012	0.00013		0.00012		0.92	
Trimethylamine	0.00014	0.00017		0.00011		0.66	
Ammonia		1.59	1.07	0.15	0.676	0.094	0.139
Hydrogen sulphide	0.0006	0.00075	0.00049	0.00050	0.65	0.66	1.02
Isobutanol	0.012	0.013		0.012		0.90	
Propionic acid	0.0021	0.0019		0.0025		1.31	

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