Effective immediately, the Toxicology Section recommends that the following values be used as interim Effects Screening Levels (ESLs) for nitrous oxide until this chemical undergoes formal ESL development under RG-442 (TCEQ 2006). These interim ESLs are five times higher than the previous nitrous oxide ESLs published on the 2003 Effects Screening Level List.

### Background

In 1993, the short-term ESL for nitrous oxide was set at 900 μg/m³ (500 ppbv), and the long-term ESL was set at 90 μg/m³ (50 ppbv). As was typical for that time, the short- and long-term ESLs were calculated as 1 percent and 0.1 percent, respectively, of an appropriate occupational exposure limit. The basis for this ESL was the ACGIH TLV-TWA\(^1\) of 50 ppm. Supporting this TLV was a No Observed Adverse Effect Level (NOAEL) in a male human exposure study (Venables et al. 1983). In this study, 50 ppm was identified as an unbounded NOAEL for decrements in neurobehavioral performance on four psychomotor tests. This study also identified 50 ppm as an unbounded Lowest Observed Adverse Effect Level (LOAEL) for non-significant deterioration in mood (sleepiness, physical tiredness, mental tiredness, and general good health). The short-term ESL was calculated as follows:

\[
50 \text{ ppm} \times \frac{1,000 \text{ ppbv}}{1 \text{ ppm}} \times \frac{1}{100} = 500 \text{ ppbv}, \text{ and converted to } \mu g/m^3, \\
500 \text{ ppbv} \times \frac{\text{molecular weight}}{24.45} = 500 \text{ ppbv} \times \frac{44.01}{24.45} = 900 \mu g/m^3
\]

\(^1\) American Conference of Governmental Industrial Hygienists Threshold Limit Value-Time Weighted Average
The corresponding long-term ESL was set at 50 ppbv or 90 μg/m$^3$.

We are now revising the nitrous oxide ESL based on additional information which reduces the level of uncertainty in intraspecies application of the available toxicity data.

**Evaluation**

In a study of male volunteers, Bruce and Bach (1976) identified 25 ppm nitrous oxide (with co-exposure to 1 ppm halothane) as a NOAEL for seven psychological tests. In the same study, 50 ppm was identified as a LOAEL for measurable and statistically significant decrements in performance of two of those psychological tests (i.e., two audiovisual tests). It has come to our attention that the Bruce and Bach (1976) study volunteers represented a sensitive subpopulation with regard to effects of nitrous oxide exposure. Most of the volunteers who participated in that study were Mormons who, because of their avoidance of stimulants and depressants (e.g., tobacco, coffee, tea, alcohol, and sometimes chocolate), might have been unusually sensitive to depressant chemicals such as nitrous oxide. This fact was not initially known to the study’s authors but was subsequently published (Bruce and Stanley 1983; Bruce 1991).

Because of the inadvertent sampling bias, the conclusions drawn in the Bruce and Bach (1976) paper are not applicable to the general population and are considered to be an inappropriate basis for an occupational exposure limit (Bruce 1991). However, this study on human volunteers who are believed to represent a sensitive subpopulation is especially relevant to the derivation of an ESL which is intended to protect the general population including sensitive subgroups. In particular this study supports the use of an intraspecies uncertainty factor (UF) of 3 rather than the default of 10. Using the NOAEL in humans negates the necessity of LOAEL-to-NOAEL and interspecies UFs. A factor of 0.3 is applied in consideration of aggregate and cumulative exposure, and thus, an interim short-term ESL is calculated as follows:

$$25 \text{ ppm} \times \frac{1,000 \text{ ppbv}}{1 \text{ ppm}} \times \frac{1}{3} \times 0.3 = 2,500 \text{ ppbv}, \text{ and converted to } \mu g/m^3,$$

$$2,500 \text{ ppbv} \times \frac{\text{molecular weight}}{24.45} = 2,500 \text{ ppbv} \times \frac{44.01}{24.45} = 4,500 \mu g/m^3$$

For modeling purposes the default interim long-term ESL is 250 ppbv or 450 μg/m$^3$.

If you have any questions regarding this evaluation, please do not hesitate to contact me at 512-239-1784 or vleopold@tceq.state.tx.us.

**References**