



The OSPA Toxicology Working Group on Glycol Ethers has reviewed the AFSSET report on beta-propylene glycol methyl ether, entitled: "Impuretés toxiques pour la reproduction dans les produits contenant du 1-méthoxy-propanol-2-ol ou son acétate", dated July 2007.

We have addressed the toxicology data and NOELs used, the concentration of beta-PGME in various end-user products, the model used to calculate exposures and the risk characterisation performed for the various scenarios. The following comments have been prepared.

1. Toxicology: NOELs used for beta-PGME and 2-MPA:

- To assess developmental toxicity effects of beta-PGME, AFSSET has used an NOEL of 26 mg/kg/day for 2-MPA (Carney et al, 2003) and says that this corresponds to 37 mg/kg/day beta-PGME.
- What AFSSET does not use is the real NOEL for beta-PGME from the BASF inhalation teratology study in rabbits (Merkle et al, 1987 and Hellwig et al, 1994). In the BASF study, an NOEL for developmental effects of beta-PGME of 145 ppm was identified, which corresponds to **58 mg/kg/day**. The latter figure should be used for the risk characterisation.
- To assess the reproduction toxicity effects of beta-PGME, AFSSET takes the NOEL of the 2-generation reproduction toxicity study on PGME (Carney et al, 1999, being 1000 ppm (corresponds to 1325 mg/kg/day) and then takes 2% of this value for the NOEL of beta-PGME, i.e. being 26 mg/kg/day.

2. The concentration of beta-PGME in products on the market

- AFSSET identifies in their report 4 categories of products via which the general public potentially can be exposed to beta-PGME. These are: consumer products (general), aqueous paints, varnishes, detergents & cleaners and solvents. They assume - based on information from INERIS, INSERM, EU Risk Assessment reports - that the maximum level of PGME in these products is 20%.
- AFSSET uses in their calculations various levels of beta-PGME in marketed products: 0.06%, 0.3% and 0.5%. AFSSET justified these levels as follows: 0.5% is the maximum level of beta-PGME in commercial PGME, 0.3% is probably the actual level in most commercial PGME samples, and 0.06% is the actual level of beta-PGME in products like paints which contain 20% PGME. AFSSET has chosen to conduct the risk characterisations assuming 0.5% of beta-PGME and has ignored that actual levels in products, to which the public is potentially exposed, are much lower!
- In the assessment of indoor air exposure of the public to beta-PGME, AFSSET calculates for exposure via generic consumer products with a level of 0.5% beta-PGME being present in end-products. This is not correct as this the maximum level of beta-PGME in commercial PGME. The maximum level of beta-PGME in end-products should, therefore, be **< 0.1%**.
- For paints & varnishes, AFSSET calculates with 0.06, 0.3 and 0.5% for inhalation exposure and with 0.5% for dermal exposure. Although AFSSET performed all these calculations, for the total exposure (inhalation and dermal combined), they only considered the calculation with 0.5% of beta-PGME.



- For detergents & cleaners), AFSSET calculates with 0.5% both for inhalation exposure and for dermal exposure.

### 3. The Wallpaper model used to calculate exposures

- AFSSET refers to data created with EGBE, using the EPA Wallpaper model for inhalation exposure to paints, but actually admits in their report that they have no experience with it! AFSSET just uses the EGBE data (from the EU risk assessment) and extrapolates to beta-PGME. This is not an appropriate, scientific approach.
- We have applied the Wallpaper model with beta-PGME and have made the following observations:
  - AFSSET copied the parameters for EGBE into their beta-PGME report. We noted that the parameters they used are not similar to the default parameters described in the EPA model for the "Residents Do-it-your self" module.
  - In the AFSSET report it is not mentioned how much the building volume is: this could have a substantial influence on the air concentration of PGME.
  - So far the worst case is the Acute Potential Dose Rate (highest dose in 24 hours) and for that one the numbers do not differ too much using the different parameters (Wallpaper default vs AFSSET). Whether the Wallpaper default settings are used or the AFSSET parameters, in industry's calculations using beta-PGME, all estimated exposure values are far below the values mentioned in the AFSSET report.
- Interestingly, the numbers for the 24-hour external dose (mg/kg/day) in the AFSSET report do almost exactly match the air concentrations (mg/m<sup>3</sup>) that industry has calculated using the AFSSET parameters. We also used the Wallpaper model for products containing 0.1% beta-PGME.

	<u>Industry (Wallpaper)</u>	<u>AFSSET report</u>	<u>Real exposure should be</u>
0.5% beta-PGME	3.24 mg/m <sup>3</sup>	3.3 mg/kg/day	<b>0.13 mg/kg/day</b>
0.3% beta-PGME	1.94 mg/m <sup>3</sup>	1.98 mg/kg/day	<b>0.07 mg/kg/day</b>
0.06 beta-PGME	0.389 mg/m <sup>3</sup>	0.396 mg/kg/day	<b>0.02 mg/kg/day</b>
0.1% beta-PGME	0.469 mg/m <sup>3</sup>	not done	<b>0.0255 mg/kg/day</b>

### 4. Risk Characterisation by AFSSET

- In the AFSSET report the risk characterisation was prepared for:
  - Pregnant women, 24 hours exposed: concern is "developmental effects". For the risk characterisation, the NOEL of 26 mg/kg/day from the rabbit 2-MPA study was used, with a default uncertainty factor of 100. AFSSET used the 3 levels of beta-PGME (0.06, 0.3 and 0.5%) for the exposure calculations. The MOS values (total, combined exposure) for the various products (containing 0,5% beta-PGME), were:

indoor air: MOS = 152941  
 paints & varnishes: MOS = 8 **(this is a scenario of concern as the MOS is < 100)**  
 detergents & cleaners: MOS = 234

For the scenario paints & varnishes, the MOS for products containing 0.06 and 0.3% beta-PGME were **52** and **12**, respectively. **So paints & varnishes were identified as a risk scenario for pregnant women.**

- Men, daily exposed during 14-days (and 2 events in these 14 days): concern is "effect on sperm". For the risk characterisation, the NOEL of 26 mg/kg/day from the 2-generation

reprotox study in rat was used with a default uncertainty factor of 16. AFSSET calculated exposures with 0.5% beta-PGME in products. The MOS values were:

indoor air: MOS = 152941  
paints & varnishes: MOS = 55  
detergents & cleaners: MOS = 327

- Men, daily exposed during 365 days (and 10 events per year) :concern is "effect on sperm". For the risk characterisation, the NOEL of 26 mg/kg/day from the 2-generation reprotox study in rat was used with a default uncertainty factor of 16.

indoor air: MOS = 152941  
paints & varnishes: MOS = 279  
detergents & cleaners: MOS = 342

For men, AFSSET determined the total MOS (from combined exposure to indoor air, paints & varnishes and detergents & cleaners) to be **154**. So, no risk of beta-PGME was identified for men for the endpoint "effects on sperm".

#### 5. Industry approach for risk characterisation of beta-PGME

- We have restricted ourselves to comment on the scenario of concern: pregnant women exposed to paint & varnishes.
  - First of all, the NOEL for developmental effects of beta-PGME to be used is: **58 mg/kg/day**.
  - The level of beta-PGME in paints & varnishes: **maximum 0.1%**
  - Worst case inhalation exposure from paint & varnishes using the Wallpaint model is **0.0255 mg/kg/day**
  - Dermal exposure estimate (with EASE and 30% absorption rate): 0.021 mg/kg/day

Total exposure (combined) would be: **0.0465 mg/kg/day**. This would result in a **MOS of 1250** for this scenario.

#### CONCLUSION

In industry's opinion, the AFSSET report on beta-PGME contains a number of serious scientific mistakes which have resulted in a totally inappropriate estimate of the risk of pregnant women to a small impurity (beta-PGME), present in commercial products formulated with PGME.

Dr. Jan Wilmer  
Chairman of the OSPA Toxicology WG on Glycol Ethers

23 November 2007

## Reference list

Several critical studies are missing in the reference list of the AFSSET report, in particularly the BASF (published) studies on beta-PGME.

Fundam Appl Toxicol. 1994 Nov;23(4):608-13. s

### **Prenatal toxicity of inhalation exposure to 2-methoxypropanol-1 in rabbits.**

**Hellwig J, Klimisch HJ, Jäckh R.**

Department of Toxicology, BASF Aktiengesellschaft, Federal Republic of Germany.

2-Methoxypropanol-1 was investigated for prenatal toxicity in Himalayan rabbits after inhalation exposure to 0, 145, 225, 350, and 545 ppm for 6 hr per day from Gestation Day 6 through 18. Maternally toxic effects were found with decreased body weights from Day 12 of gestation through the end of the study at 545 ppm. A dose-dependent increase of resorptions, fetal malformations, and variations was observed at 225, 350, and 545 ppm, whereas 145 ppm was devoid of exposure-related effects. The malformation rate at 545 ppm was 100%. The types of malformations mainly consisted of absent phalanges and absent or rudimentary metatarsal bones, malformed ribs, and a unique enlargement of sternebrae. The effects are very similar to those previously found with 2-methoxypropylacetate-1. The results of this study may have implications for the quantitative estimation of risks associated with 2-methoxypropanol-1 impurities in the widely used isomer 1-methoxypropanol-2 which itself does not show developmental toxicity.

Fundam Appl Toxicol. 1987 Jan;8(1):71-9

### **Prenatal toxicity of 2-methoxypropylacetate-1 in rats and rabbits.**

**Merkle J, Klimisch HJ, Jäckh R.**

2-Methoxypropylacetate-1 was investigated in Wistar rats and Himalayan rabbits for embryotoxic potential. Rats after inhalation exposure to 0, 0.6, 3.0, or 14.9 mg/liter (approximately 0, 110, 550, or 2700 ppm, respectively) for 6 hr per day from gestation Days 6 through 15 exhibited some degree of maternal toxicity at 2700 and 550 ppm. At 2700 ppm an increase of skeletal anomalies of the thoracic vertebrae among the fetuses was observed and interpreted as an exposure-related slight teratogenic effect. In Himalayan rabbits exposed via inhalation to 0, 0.2, 0.8, or 3.0 mg/liter (approximately 0, 36, 145, or 550 ppm, respectively) for 6 hr per day from gestation Days 6 through 18 teratogenicity was much more pronounced: at 550 ppm, in the absence of clear maternal toxicity, the fetuses of all litters showed severe malformations. No maternal or fetal effects were observed at 145 and 36 ppm. Dermal application of 1000 and 2000 mg/kg to Himalayan rabbits from gestation Days 6 through 18 failed to produce maternal or fetal toxicity.

PMID: 3556824 [PubMed - indexed for MEDLINE]

Hum Exp Toxicol. 2005 Feb;24(2):95-9.

### **Investigations on the subchronic toxicity of 2-methoxypropanol-1(acetate) in rats.**

**Ma-Hock L, Klimisch HJ, Gembardt C, Deckardt K, Jäckh R.**

BASF Aktiengesellschaft, Product Safety, Ludwigshafen, Germany.

Wistar rats were exposed to 2-methoxypropylacetate-1 (2-MPAc-1) vapours in concentrations of 0, 110, 560 and 2800 ppm for (equiv. to 0; 0.6; 3.0 and 14.9 mg/L) for 4 weeks in chambers (6 hours/day; 5 days/week; five male and five female animals per group). The top concentration was equivalent to a 95% vapour saturation at 20 degrees C and the animals reacted to this with a moderate respiratory irritation during the 6 hours exposure times; at 560 ppm these effects were only slight. The top dose was also associated with a significantly reduced body weight development and some hematologic and biochemical alterations of little specificity. The most prominent effect was thymic atrophy. No effects were noted on the testes or on the cellularity in blood or bone marrow. 560 ppm were without systemic effects. Furthermore, 2-methoxypropanol-1 (2-MP-1), 2-

MPAc-1 and 2-ethoxyethanol (EE) were administered in parallel by gavage to groups of five male Wistar rats daily for 10 days at near equimolar dose levels (1800, 2600 and 1800 mg/kg per day, respectively). At the end of the administration period the testes were investigated. There was a pronounced testicular atrophy in animals exposed to EE, whereas no adverse effects were observed with 2-MP-1 and 2-MPAc-1. The results of these studies indicate that 2-MP-1 and 2-MPAc-1 which previously had been shown to exert pronounced prenatal toxicity in rabbits and weak prenatal effects in rats are devoid of other forms of systemic toxicity in rats that are typically observed with ethoxyethanol and methoxyethanol.