Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

Methanol

EC Number: 200-659-6
CAS Number: 67-56-1

CLH-O-0000004421-84-03/F

Adopted

12 September 2014

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OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of Regulation (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonized classification and labelling (CLH) of:

Chemical name: **Methanol**

EC Number: **200-659-6**

CAS Number: **67-56-1**

The proposal was submitted by **Italy** and received by RAC on **09 October 2013.**

In this opinion, all classifications are given in the form of CLP hazard classes and/or categories, the majority of which are consistent with the Globally Harmonized System (GHS). The classification notation for 67/548/EEC, the Dangerous Substances Directive (DSD) is no longer provided.

PROCESS FOR ADOPTION OF THE OPINION

Italy has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation*** on **29 October 2013**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **13 December 2013**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Bert-Ove Lund**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation and the comments received are compiled in Annex 2. The RAC opinion on the proposed harmonized classification and labelling was adopted on **12 September 2014** by consensus.

OPINION OF THE RAC

The RAC adopted the opinion on **Methanol** that should be classified and labelled as follows:

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard Statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Entry	603-001-00-X	methanol	200-659-6	67-56-1	Flam. Liq. 2 Acute Tox. 3 * Acute Tox. 3 * Acute Tox. 3 * STOT SE 1	H225 H331 H311 H301 H370**	GHS02 GHS06 GHS08 Dgr	H225 H331 H311 H301 H370 **		* STOT SE 1; H370: C ≥ 10 % STOT SE 2; H371: 3 % ≤ C < 10 %	
Dossier submitters proposal	603-001-00-X	methanol	200-659-6	67-56-1	**Add** Repr. 1B	**Add** H360D	-	**Add** H360D			
RAC opinion	603-001-00-X	methanol	200-659-6	67-56-1	-	-	-	-		-	
Resulting Annex VI entry if agreed by COM	603-001-00-X	methanol	200-659-6	67-56-1	Flam. Liq. 2 Acute Tox. 3 * Acute Tox. 3 * Acute Tox. 3 * STOT SE 1	H225 H331 H311 H301 H370**	GHS02 GHS06 GHS08 Dgr	H225 H331 H311 H301 H370 **		* STOT SE 1; H370: C ≥ 10 % STOT SE 2; H371: 3 % ≤ C < 10 %	

RAC evaluation of reproductive toxicity

Summary of the Dossier submitter's proposal

The proposal for classification was based on weight of evidence from all of the available studies. Severe developmental effects were consistently recorded in both rats and mice in the absence of maternal toxicity. In general, prenatal developmental toxicity was evidenced in these species by decreased foetal weight, decreased incidence of live foetuses and increased incidences of resorptions and dead foetuses (relative to concurrent controls), as well as teratogenic effects (neural tube defects, cleft palate and skeletal and visceral malformations). Moreover, post-natal effects (some of which were observed at maternally toxic dose levels) included increased neonatal mortality and growth retardation and earlier testis descent. A recent, non-GLP, test guideline compliant study in rabbits (Sweeting *et al*., 2011) suggested that methanol may also act as a teratogen in non-rodent species with a metabolic pathway for methanol more similar to humans, albeit the potency might be lower than in rodents. Moreover, in *Macaca fascicularis*, methanol significantly reduced the duration of pregnancy, suggesting that pregnancy also represents a life stage susceptible to methanol exposure in primates. Classification as Repr. 1B – H360D was therefore proposed.

Comments received during public consultation

Three Member State Competent Authorities (MSCAs) supported the proposal. A fourth MSCA opposed the proposed classification based on the large differences in the metabolic pathways of methanol in rodents and humans, and instead suggested classification as Repr. 2, pending a more detailed description of the studies and a more substantial justification.

Three individuals commented on the proposal, with one supporting and two opposing the proposal.

Six industry organisations opposed the proposal. There were two main reasons for the objections. The first concerned kinetic differences (metabolic pathways) between species, making rodents very poor models for methanol toxicity in humans. Accordingly, the CLP guidance uses methanol as an example of when rat data should not be used for classification purposes (concerning acute toxicity and STOT SE). The second reason concerned the very high acute and specific toxicity of methanol in humans, resulting in severe toxicity before reaching such blood concentrations of methanol that led to developmental toxicity in rodents. Based on these arguments, methanol should not be classified for developmental toxicity at all according to the industry organisations.

Assessment and comparison with the classification criteria

<u>Kinetics/metabolic pathways</u>

The kinetic differences between rodents and humans can be explained by their different sets of enzymes for metabolising methanol, leading to different metabolic rates and different metabolites in rodents and humans. Briefly, the first step in the metabolism of methanol is mediated by catalase and alcohol dehydrogenase in rodents and by alcohol dehydrogenase in primates. The rate-limiting step in rodents is the formation of formic acid, whereas in primates it is the further degradation of formic acid. This results in methanol accumulating in the blood of rodents, while formic acid and methanol accumulate in human blood.

In the human population, it is known that polymorphism in alcohol dehydrogenases exist, leading to differences in sensitivity to Methanol both at the individual level and also at the population level. It can be speculated that sensitivity to methanol toxicity is also affected by such polymorphisms.

Toxicity – human data

There was only one human case reported in the CLH dossier with exposure to "methanol only" (single exposure to 250-500 ml) during late pregnancy, with no effects on the child.

There is, however, more general experience of the acute effects of methanol in humans. The formic acid formed in humans may lead to acidosis, explaining the possibly 10-fold higher acute toxicity of methanol in humans than in rodents. In addition, eye toxicity (potentially leading to blindness) is a very characteristic effect in humans, occurring even at low exposure levels. According to IPCS (2001), acute ingestion of as little as 4 to 10 mL of methanol may cause permanent blindness, but individual susceptibility varies widely, possibly because of the frequent concurrent ingestion of ethanol.

Toxicity – animal data

There are a large number of studies in rats and mice clearly showing developmental toxicity after both oral and inhalation exposure to methanol. I It appears form the dossier that methanol exposure may cause decreased foetal weight, decreased incidence of live foetuses, increased incidences of resorptions, dead foetuses, exencephaly, neural tube defects, cleft palate and skeletal and visceral malformations. However, according to the CLH dossier, the lowest LOAELs/LOAECs were in the order of 1000 mg/kg (1.3 mL/kg) and 5000 ppm, respectively. It is noted that other evaluations have used a mouse developmental toxicity study giving a LOAEC of 2000 ppm as the critical study (inhalation exposure during gestation day (GD) 6-15) (Rogers *et al.*, 1993). The rodent studies showed developmental toxicity, but with a low potency as indicated by the high LOAELs/LOAECs, and the question remains how relevant the rodent data are for humans in the light of the differences in kinetics.

There were also studies in two non-rodent species, which have metabolic pathways more or less similar to the human metabolism of methanol (Sweeting *et al.,* 2010), and which might be important for the assessment of human relevance of the developmental toxicity noted in rodents.

Sweeting *et al.* (2011) dosed rabbits intra-peritoneally with two doses of 2000 mg/kg methanol on GD 7 or 8, and sacrificed the dams at GD 29. The dossier refers to a 4-fold increase in tail abnormalities (short or absent) as the only finding, but RAC notes that the observation was not statistically significant and the poorly reported study is therefore of questionable relevance. The potential methanol-induced developmental toxicity during other parts of the rabbit gestation (than GD 7-8) has not been studied.

Burbacher *et al.* (2004) studied the effects of methanol inhalation (0, 200, 600, 1800 ppm for 2.5 hours daily) on monkeys (*Macaca fascicularis*) for 180 days prior to and throughout their pregnancy. A full study report was published in 1999 by the Health Effects Institute (Burbacher *et al.,* 1999), and the study was later also published in the scientific literature (Burbacher *et al.,* 2004). The four findings included pregnancy complications, shortened pregnancy period, developmental neurotoxicity, and a wasting syndrome. The CLH report contained very limited information, simply concluding that "*methanol exposure was associated with a delay in early sensorimotor development for male infants of all dose groups and with deficits in visual recognition memory for all infants of all dose groups*". Based on this minimal reporting, it was not possible to judge if there is a dose-response relationship (incidence, severity) and thus whether these are substance-related effects. Also, it was not clear whether the effects, if any, should be considered adverse. Therefore, the full study report (Burbacher *et al.,* 1999) was consulted.

Five methanol-exposed females were caesarean-sectioned due to pregnancy complications (uterine bleedings in 4 females) and prolonged unproductive labour (1 female). Although these complications were not observed in the control group, the findings were not dose-dependent or statistically significant, as the incidences were 2 at the low dose, 2 at the mid dose, and 1 at the high dose (out of 8-9 animals per group).

The mean duration of pregnancy in the methanol-exposed groups was significantly decreased, by 6-8 days when compared to controls. However, there was no dose-response relationship, as the durations of pregnancy were 168, 160, 162, and 162 days in the control, low, medium, and high

dose groups, respectively. Furthermore, the duration of pregnancy was within the reported normal range for this species (NTP-CERHR, US NTP 2003).

There were no effects on birth weight, growth or health of the infants. Eight different behavioural tests were conducted, with six of them negative. Infant sensorimotor development was assessed by determining the age when infants successfully reached for and retrieved a small object in full view in order to receive a reward. There were no effects of the methanol exposure on the female infants (34, 33, 28, and 40 days in the control, low, medium, and high dose groups, respectively). However, in males there appeared to be an effect of the methanol exposure, with statistically significant delays in the mid and high dose groups (24, 32, 43, and 40 days). However, it should be noted that the group sizes for the males were 3, 5, 3, and 2 infants in the control, low, medium, and high dose groups, respectively. Thus, this finding should be interpreted with caution.

The other test that possibly indicated an effect was a test for infant recognition memory, where the infant's ability to recognise previously seen stimuli from those that were new was assessed. The testing was conducted using two cohorts (3-4 infants/group), with an effect in one (0.70, 0.61, 0.50 and 0.60 in the control, low, medium, and high dose groups, respectively) but not the other cohort. After combining the cohorts, a statistically significant effect only remained in the mid-dose group and a relationship with exposure to the substance can thus be questioned.

An unexpected finding was that at the age of 1-1.5 years, 2 female offspring out of 7 in the high dose group started to suffer from a wasting syndrome, requiring euthanasia when they reached the age of 20 and 36 months, respectively.

An overall assessment of the monkey studies indicated that methanol may have affected the infants, but that the data were not very robust and clearly not sufficient for classification. Furthermore, there were minimal similarities between the very clear effects noted in rodents and those possibly observed in the monkeys. It is acknowledged that the monkey exposure levels ($\leq$1800 ppm) and exposure time per day (2.5 hours in monkey vs 7 hours in mice), were lower than the LOAEC of 2000 ppm in mice, and the blood methanol concentration was 35 mg/L at the top dose in monkeys when compared to 537 mg/L in mice at the LOAEC. Therefore, developmental toxicity also in monkeys at higher exposure levels cannot be ruled out.

The RAC concludes that there is robust evidence of developmental toxicity of methanol in rodents, but very limited indications of developmental toxicity from non-rodent species which have metabolic pathways more similar to humans. In addition, it is noted that the findings of developmental toxicity in rodents only occur at high exposure levels (with lowest LOAELs/LOAECs of 1000 mg/kg (Youssef, 1997) and 2000 ppm (Rogers, 1993), via the oral and inhalation route, respectively).

Comparison with the criteria

Substances are classified in Category 1 for reproductive toxicity when they are known to have produced an adverse effect on development in humans or when there is evidence from animal studies to provide a strong presumption that the substance has the capacity to interfere with reproduction in humans. The classification of a substance is further distinguished on the basis of whether the evidence for classification is primarily from human data (Category 1A) or from animal data (Category 1B).

There is no indication from human experience of developmental toxicity of methanol, and Category 1A is therefore not appropriate.

Classification in Category 1B is largely based on data from animal studies, providing clear evidence of an adverse effect on sexual function and fertility or on development in the absence of other toxic effects. Although methanol causes developmental toxicity in rodents, there are limited indications of developmental effects in non-rodent species having metabolic pathways for methanol more similar to those occurring in humans. The relevance of extrapolating rodent toxicity data to humans can therefore be questioned. Accordingly, the CLP guidance concludes that rat acute toxicity data is of no relevance for humans, because there is human evidence of a much higher acute toxicity of methanol than in rodents, presumably caused by the formic acid that is formed in humans but not in rodents. It is also noted that developmental toxicity in rodents

only occurs at high exposure levels, and it is possible that such high exposure levels would generate such high blood concentrations of formic acid in humans that maternal toxicity (acidosis, blindness, lethality) would occur. Taken together, the RAC is of the opinion that the rodent data are not sufficient to presume similar effects in humans, and a classification with Category 1B is therefore not appropriate.

Category 2 is an option when there is some evidence from experimental animals of an adverse effect on development that are not secondary non-specific consequences of other toxic effects. There was clear evidence of developmental toxicity in rodents, whereas the findings from monkeys and rabbits were not sufficient for classification. The mouse appeared to be the most sensitive species to the developmental toxicity of methanol, but it is noted that rodents have a different metabolism of methanol than humans.

A comparison of methanol blood concentrations in humans and rodents was conducted with the aim to establish whether methanol concentrations sufficiently high to cause developmental toxicity can arise in humans without simultaneously resulting in acutely toxic formate concentrations (see also the section 'Supplemental Information - In depth analyses by RAC'). It appears that in humans, blood concentrations similar to those seen in mice at inhalation concentrations leading to developmental toxicity findings which clearly meet the classification criteria (cleft palates were observed at 5000 ppm and a blood concentration of 1650 mg methanol/L), would be lethal. Blood concentrations similar to those in the mouse at the LOAEC (increased incidence of cervical rib anomalies) would, in humans, be accompanied by signs of acute methanol intoxication (caused by formate). These signs could be nasal irritation, nausea, blurred vision, and mild CNS depression 6-30 hours later (NAS/COT Subcommittee for AEGLs (2005)) in severe cases, followed by acidosis and impaired vision (blindness). At an exposure level equivalent to the mouse NOAEC (1000 ppm), only slight effects may arise in humans.

If this comparison was conducted using the rat LOAEC for developmental toxicity, such methanol concentrations may be acutely lethal to humans.

There are known differences among individuals and populations with respect to the availability of alcohol dehydrogenase (polymorphism), but there are also different isozymes of alcohol dehydrogenase that contribute to the metabolism of methanol, and additionally other enzymes operating in other steps of the metabolism, making it difficult to predict the overall consequences of enzymatic variations on the overall toxicity of methanol.

The above comparison indicates that methanol blood levels causing clear developmental toxicity in rodents would be acutely **toxic or even lethal to humans. Thus, classification for developmental toxicity seems not relevant. The RAC therefore concludes that, based on the available information, there is not sufficient evidence for classifying methanol for developmental toxicity.**

Additional references

International Programme on Chemical Safety (IPCS) (2001). Methanol, Poisons Information Monograph 335.

NAS/COT Subcommittee for AEGLs (2005). Interim acute exposure guideline levels (AEGLs) for METHANOL (CAS Reg. No. 67-56-1).

US NTP (2003). NTP-CERHR monograph on the potential human reproductive and developmental effects of methanol). [http://ntp.niehs.nih.gov/ntp/ohat/methanol/methanol_monograph.pdf]

Rogers *et al*. (1993). The developmental toxicity of inhaled methanol in the CD-1 mouse, with quantitative dose-response modeling for estimation of benchmark doses. Teratology 47: 175-188.

US EPA (2013). US EPA Toxicological review of methanol [http://www.epa.gov/iris/subst/0305.htm]

Annex 1 The Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in 'RAC boxes'.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and RAC (excluding confidential information).