Committee for Risk Assessment (RAC)

Opinion

on an Annex XV dossier proposing restrictions on

Methanol

ECHA/RAC/RES-O-0000006324-78-01/F

Adopted

4 December 2015

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Opinion of the Committee for Risk Assessment

on an Annex XV dossier proposing restrictions of the manufacture, placing on the market or use of a substance within the EU

Having regard to Regulation (EC) No 1907/2006 of the European Parliament and of the Council 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (the REACH Regulation), and in particular the definition of a restriction in Article 3(31) and Title VIII thereof, the Committee for Risk Assessment (RAC) has adopted an opinion in accordance with Article 70 of the REACH Regulation and the Committee for Socio-economic Analysis (SEAC) has adopted an opinion in accordance with Article 71 of the REACH Regulation on the proposal for restriction of

Chemical name(s):	**Methanol**
EC No.:	**EC No 200-659-6**
CAS No.:	**CAS No 67-56-1**

This document presents the opinions adopted by RAC and SEAC. The Background Document (BD), as a supportive document to both RAC and SEAC opinions, gives the detailed ground for the opinions.

PROCESS FOR ADOPTION OF THE OPINIONS

Poland has submitted a proposal for a restriction together with the justification and background information documented in an Annex XV dossier. The Annex XV report conforming to the requirements of Annex XV of the REACH Regulation was made publicly available at http://echa.europa.eu/web/guest/restrictions-under-consideration on ***18 March 2015***. Interested parties were invited to submit comments and contributions by ***17 September 2015.***

ADOPTION OF THE OPINION

Rapporteur, appointed by RAC: ***Veda Varnai***

Co-rapporteur, appointed by RAC: ***Lina Dunauskiene***

The RAC opinion as to whether the suggested restrictions are appropriate in reducing the risk to human health and/or the environment has been reached in accordance with Article 70 of the REACH Regulation on ***5 December 2015***

The RAC opinion was adopted ***by consensus.***

OPINION

The proposal of the Dossier Submitter:

Methanol CAS No 67-56-1 EC No 200-659-6	Shall not be placed on the market for supply to the general public: – as a constituent of windshield washing fluids (including windshield defrosters) in concentration equal to, or greater than 3.0% by weight, – as an additive to denatured alcohol (*methylated spirit, brennspiritus*) in concentrations equal to, or greater than 3.0% by weight. Member State may maintain any existing and more stringent restrictions for methanol.

THE OPINION OF RAC

RAC has formulated its opinion on the proposed restriction based on information related to the identified risk and to the identified options to reduce the risk as documented in the Annex XV report and submitted by interested parties as well as other available information as recorded in the Background Document. RAC considers that the proposed restriction on ***methanol*** is the most appropriate EU wide measure to address the identified risks in terms of the effectiveness in reducing the risks provided that the conditions are modified.

The conditions of the restriction proposed by RAC are:

Substance	**Conditions of the restriction**
Methanol CAS No 67-56-1 EC No 200-659-6	Shall not be placed on the market for or used by the general public: – as a component of windshield washing fluids (including windshield defrosters) in concentration equal to or greater than 0.6% by weight, – as a component[1] of denatured alcohol (*methylated spirit, brennspiritus*) in concentration equal to or greater than 0.6% by weight.

No derogations are proposed by the Dossier Submitter.

It is suggested that the statement contained in the scope proposed by the Dossier Submitter to the effect that *'Member State may maintain any existing and more stringent restrictions for methanol*' be removed, as the Commission has pointed out that this is *not foreseen by the present EU legislation*.

A transition period of 3 months is proposed.[2]

[1] The term 'constituent' has been proposed by the Forum; indeed, the Guidance on Substance Identification uses the terms constituent for a*ny single species present in a substance that can be characterised by its unique chemical identity* and component for *substance intentionally added to form a mixture*. This has been reflected in the RAC proposal.

[2] To be fixed after the end of Public Consultation and following discussions at SEAC.

JUSTIFICATION FOR THE OPINION OF RAC

IDENTIFIED HAZARD AND RISK

The aim of the Dossier Submitter's proposal is to reduce the incidence of severe methanol poisoning following deliberate misuse of windshield washing fluids and denatured alcohol containing methanol, by chronic alcoholics and sporadically by non-alcoholics (e.g. binge drinking in adolescents) which are used as a cheap substitute for consumable alcohol. The proposed restriction is also expected to prevent methanol poisoning following accidental ingestion of windshield washing fluids and denatured alcohol, including poisonings in children.

The proposal therefore seeks to limit methanol concentration in windshield washing fluids and denatured alcohol, which are considered to be the principle products that could contain high a percentage of methanol and are recognised as the type of methanol-containing products most frequently linked to methanol poisoning in the general population.

Intentional misuse of substances and mixtures is usually not considered in the exposure estimation process. However, if targeted by the Dossier Submitter in a REACH Restriction, it may be considered in the Annex XV dossier if it relates to known exposure that creates a serious concern for human health or the environment to be addressed at Union level, and there is no other appropriate EU legislation to tackle the problem (see Guidance text below).[3]

RAC concludes that this restriction proposal by presenting the data on severe cases of poisonings following abuse of methanol-containing products in several EU countries fulfils this requirement. It could also be argued that although ingestion of methanol-containing products by alcohol addicts is intentional, it does not have the aim of self-poisoning, but it is a part of clinical feature of addictive behaviour in chronic alcoholism.

- Description of and justification for targeting of the information on hazard and exposure

In certain EU countries (e.g. Poland, Finland, Bulgaria) significant numbers of methanol poisoning cases, including those with a lethal outcome (e.g. on average 25 deaths per year for the period from 1995-2012 in Finland) have been reported. When ingestion of adulterated consumable alcohol is excluded, the most common cause of methanol poisoning was ingestion of methanol-containing products available for consumer use. These products are mainly consumed by alcoholics as a surrogate for much more expensive (excisable) consumable alcohol.

There are over 100 methanol-containing products available for consumer use on the EU market, including cleaning agents, solvents, paints, lacquers and/or varnishes, fuels, corrosion inhibitors, biocides, adhesives, glues and binding materials, fragrances, and anti-freeze products. However, the proposed restriction only refers to two types of products, windshield washing fluids and denatured alcohol (*methylated spirit, brennspiritus*), since these two types of products, which can contain methanol in high concentration, represent the most common causes of severe methanol poisonings according to available data from the Poison Control/Information Centres in Poland and Finland. The Forum has suggested

[3] According to the Guidance on information requirements and chemical safety assessment (Chapter R.15.2.2. Reasonable worst-case situations), '*the consumer exposure estimation should normally address the intended uses of the products that contain the substances under investigation*.' The Guidance, however, recognizes that '*since consumers may not accurately follow instructions for use of products, an estimation of other reasonably foreseeable uses should be made*', and that '*the difference between other foreseeable uses and abuse can in certain cases be small*'. In such situation, '*the assessor should provide clear argumentation why a certain exposure situation is included*'.

including windshield defrosters as a sub-group of windscreen washing fluids and this advice has been followed by RAC.

- Description of the risk to be addressed by the proposed restriction

o Information on hazard(s)

Only data on methanol toxicity in humans are taken into account in this opinion. In this particular case, RAC regards animal data as being of limited use in the assessment of methanol toxicity to humans, due to significant differences in methanol metabolism and susceptibility to methanol toxicity between humans and animals (especially rodents).

In humans, methanol is metabolised to formaldehyde by hepatic alcohol dehydrogenase, which is a saturable rate-limiting process. Formaldehyde is oxidised by aldehyde dehydrogenase to formic acid or formate, depending on the pH, which is then further detoxified by a folate-dependent pathway to carbon dioxide and water. This last reaction step is also of limited capacity which may lead to a disproportionate increase of formic acid/formate in the blood and consequent metabolic acidosis.

Initial symptoms of methanol intoxication often include ataxia, sedation, and disinhibition, and, after a latent period (usually 12 to 24 hours), could be followed by headache, nausea, vomiting, abdominal and muscle pain, dizziness, visual disturbances (blurring, photophobia, constriction of the visible field, changes in colour perception, reduced visual acuity, temporary or permanent blindness), drowsiness, loss of consciousness and death. The principal clinical feature is severe metabolic acidosis of anion-gap type, largely attributed to the formic acid formation.

Based on information on methanol poisoning in humans, the Dossier Submitter (DS) proposed lethality as the point of departure (POD), and chose 0.3 g/kg body weight (bw) as a minimal acute lethal dose of ingested methanol, according to IPCS/WHO (1997).

In the Background Document, an acute oral DNEL of 0.008 g/kg bw for the general population is described according to calculations performed in the Registrant's Chemical Safety Report for methanol. This was derived from an OEL of 260 mg/m^3 (aimed at protecting workers from acute systemic and local irritation effects of methanol inhalation). This OEL is considered to be, in the majority of cases, also protective from very slight, sub-clinical CNS effects of methanol inhalation, which are reported to start to appearing at 270 mg/m^3 (FIOH 2008). However, as mentioned above, the Dossier Submitter based the risk assessment on minimal acute oral lethal dose of 0.3 g/kg bw (quoted in IPCS/WHO 1997 document) without applying an assessment factor.

RAC, however, considers that severe ocular toxicity (including blindness or severely diminished visual acuity) should be considered as a POD as it represents a serious non-lethal adverse effect.

Based on information provided in the Background Document and the data on methanol poisoning cases in humans published in the open literature (Table 1), a minimal methanol oral dose leading to severe ocular toxicity (vision limited to finger-counting at the time of discharge from hospital) was identified to be 0.26 g/kg bw. It originates from a case report of a 34-year-old woman ingesting 50 ml of bootleg whiskey with 35-40% of methanol and <4% of ethanol, described by Bennett et al. (1953). This dose level is related to some degree of uncertainty (issue raised by Methanol REACH Consortium during Public Consultation), since the amount of ingested methanol is stated differently in Table V (pages 450-453 of the article written by Bennett et al. 1953) and in the text of the article. Namely, in the table, the ingested methanol dose is stated as 'MeOH drunk'" in ml, ranging from 15–500 ml. From the article text, however, it could be deduced that values of 'MeOH drunk' shown in Table V do not refer to volume of pure methanol but to the amount of ingested bootleg whiskey (containing 35-40% of methanol). The article text states that 'The smallest

amount which produced a fatal result in the outbreak observed by the present authors was three teaspoons (about 15 ml) of 40% methyl alcohol. The highest dose recorded in a survivor was one pint (500 ml) of the same mixture.' The lowest value of 'MeOH drunk' in the table related to lethal outcome was indeed 15 ml, and the highest value in a survivor was 500 ml. RAC, therefore, decided to interpret ingested volume of 50 ml in Table V as an amount of ingested bootleg alcohol and not pure methanol, leading to a methanol dose of 0.26 g/kg bw related to severe ocular effects (taking into the calculation a 40% methanol mixture), instead of 0.66 g/kg bw as calculated by Methanol REACH Consortium (which interpreted 'MeOH drunk' as an amount of pure methanol ingested).

The lowest lethal oral methanol doses reported in the open literature (Table 2) were identified by RAC to be in the range of 0.45 – 0.51 g/kg bw (Bennett et al. 1953, Desai et al. 2013), namely in a similar range as the minimal dose leading to severe ocular toxicity.

Doses below 0.26 g/kg bw leading to severe ocular toxicity and below 0.45 g/kg bw leading to death in humans are published in the open literature, but, in RAC's opinion, these dose levels are too uncertain to be used as a POD[4] (please refer to the Background Document for more detailed clarification).

During Public Consultation several issues were raised regarding relevant no effect levels for lethality and permanent vision impairment following oral methanol exposure in humans.

Based on a literature search and applying PBPK modelling (IndusChemFate v2), the Methanol REACH Consortium proposed a value of 0.40 g methanol/kg bw as a protective level against ocular toxicity without co-exposure to ethanol, and of 0.50 g methanol/kg bw with co-exposure to ethanol or isopropanol. This is taking into account ocular toxicity at ingested methanol dose of 0.66 g/kg bw reported by Bennett et al. (1953); a reported methanol dose of 0.56 g/kg bw as a non-lethal dose that did not result in permanent vision damage in 84 subjects acutely exposed to methanol in a solution containing 5% methanol and 90% ethanol (Martensson et al. 1988); and 0.40 g/kg bw as methanol dose that according to PBPK modelling does not produce high levels of formic acid (related to ocular toxicity).

RAC, however, calculated the minimal oral methanol dose related to severe ocular toxicity as 0.26 g/kg bw, reported by Bennett et al. (1953) (for justification please see text above). RAC does not consider that no-effect studies abolish the relevance of low doses at which methanol toxicity was observed, but rather illustrate the wide variability in susceptibility to methanol toxicity in humans. RAC also points out that the PBPK model used in the Methanol REACH Consortium document is primarily a first tier or screening tool (Jongeneelen and Berge 2011; Jongeneelen and Berge, User manual), that there are uncertainties regarding blood formate levels related to death or permanent eye damage, and that modelling results regarding inter-individual human variability (e.g. gender, body mass, different rate of formate elimination) were not presented. For further clarification please refer to the Background Document.

Conclusion: RAC concluded to consider severe ocular toxicity (significantly reduced visual acuity at 0.26 g/kg bw) as the critical endpoint for further assessment.

It was noted that the SCLs for methanol (STOT SE 1; H370: C ≥ 10%; STOT SE 2; H371: 3% ≤ C < 10%) are based on eye toxicity (blindness) in humans.

[4] e.g. description of a poisoning case was not available (Wood and Buller 1904, Ziegler 1921, Duke-Elder 1945); significant contribution of ethanol toxicity cannot be ruled out in lethal outcome following ingestion of 0.08 g/kg bw of methanol described by Bennett et al. (1953); discrepancy in methanol blood concentration and stated amount of ingested methanol of 0.23-0.26 g/kg bw in two lethal cases described by Bennett et al. (1953).

Table 1. Methanol doses related to severe ocular toxicity in human methanol poisoning cases

Reference	**Patient(s)** [N]	**Product**	**Methanol dose**	**Ethanol level in a product**	**Exposure (single, repeated)**
Wood and Buller 1904 (summary not available)	?	wood alcohol	2 teaspoons of methanol (?) (10 ml, **7.9 g**)	?	?
Duke-Elder 1945 (summary not available) **IPCS/WHO 2001** (full document)	?	?	4 ml methanol (**3.2 g**) (?)	?	?
Bennett et al. 1953 (full article)	323 (5 with residual visual disturbances)	adulterated whiskey 35-40% methanol	50 ml bootleg whiskey, "vision limited to finger-counting", 34 yrs F (**16 g** methanol)	<4%	?
Erlanson et al. 1965 (full article)	39 yrs F (63 kg)	100% methanol for technical use (sold as ethanol)	**80 g** (blindness recovered after dialysis)	0 (?)	single (?)
Fujihara et al. 2006 (full article)	37 yrs M	industrial alcohol	100 ml/day, for 4 days, 75% methanol (**59.4 g/day, 238 g total**)	25%	repeated (4 days)
Brahmi et al. 2007 (full article)	16 (16-53 yrs) (1 blind)	cologne (65% methanol), spirits	30 – 1000 ml 65% methanol, blindness 300 ml (**154 g**, 23 yrs M)	?	?
Moschos et al. 2013 (full article)	adult M	70% methanol rubbing solution	one glass, 70% methanol (100-200 ml?, **59.4-119 g**)	?	single
Desai et al. 2013 (full article)	122 (121 M, 20-60 yrs) (32 PVD)	adulterated alcohol	? (range 100-700 ml 6.5% methanol, **up to 36 g**)	40%	?

M – male patient, **F** – female patient; PVD – permanent visual damage, (?) – dose level with high uncertainty due to lack of information

Table 2. Methanol doses related to lethal outcome in human methanol poisoning cases

Reference	Patient(s) [N]	Product	Methanol dose	Ethanol level in a product	Exposure (single, repeated)
Bennett et al. 1953 (full article)	323 (41 died)	bootleg whiskey 35-40% methanol	15 ml 40% bootleg whiskey, 20 yrs F (**4.8 g**, i.e. 0.07 g/kg bw)†	<4%	?
			50 ml bootleg whiskey, 41 yrs M and 63 yrs F (**16 g** methanol)‡		
			100 ml bootleg whiskey, 49 yrs M (**32 g** methanol)		
Erlanson et al. 1965 (full article)	49 yrs F (55 kg)	100% methanol for technical use	**90 g** (40 g + 50 g 29 h later)	- (?)	repeated (within 29 h)
Gonda et al. 1978 (abstract)	9 (2 died)	?	min. lethal dose 30 ml (**23.8 g**) (?)	?	?
Scrimgeour 1980 (abstract)	372 adult M	sold by a local pharmacy instead of methylated spirit	min. lethal dose 100 ml 82% methanol (**64.9 g**)	- (18% isopropanol)	?
IPCS/WHO 1997 (full document)	?	?	**21-70 g** (0.3-1 g/kg bw)* (?)	?	?
Girault et al. 1999 (full article)	35 yrs F	windshield washing fluid	500 ml 20% methanol (**79 g**)	?	single
Brahmi et al. 2007 (full article)	16 (16-53 yrs) (3 died)	cologne, spirits	30 – 1000 ml 65% methanol, min lethal 1000 ml (**515 g**, 27 yrs M)	?	?
Massoumi et al. 2012 (full article)	51 (children included?) (5 died)	as an ethanol substitute in illicit liquor	<50 ml (**<40 g**)	?	?
Desai et al. 2013 (full article)	122 (121 M, 20-60 yrs) (10 died)	adulterated alcohol	? (range 100-700 ml 6.5% methanol, **up to 36 g**)	40%	?

M – male patient, **F** – female patient; *Articles quoted for the dose range: Erlanson et al. 1965, Gonda et al. 1978, Röe 1955, (?) – dose level with high uncertainty due to lack of information; †Significant ethanol toxicity cannot be excluded; ‡Discrepancy in methanol blood concentration and stated amount of ingested methanol.

Since a dose-response curve and NOAEL could not be established due to the limitations of the database, RAC applied LOAEL to NAEL extrapolation, using an assessment factor (AF) of 3, in line with ECHA Guidance[5] where an assessment factor between 3 and 10 is suggested.

The Methanol REACH Consortium disagreed with the use of this assessment factor (proposing no assessment factors) since it considers that in alcohol abusers, the target population in the proposed restriction, the variability of alcohol dehydrogenases which could affect ethanol and methanol metabolism, is not present, and since from a wide database the lowest values for toxicity have been selected (Methanol REACH Consortium 2015).

RAC points out that well-known variability in methanol metabolism and toxicity in humans is in greater part related to genetic variability in folate metabolism and nutritional folate status (US EPA Toxicological review of methanol (non-cancer), September 2013), than to polymorphism in alcohol dehydrogenase (for further clarification please refer to Background Document).

Nevertheless, according to ECHA Guidance[5] the assessment factor for LOAEL to NAEL extrapolation is defined primarily according to the shape and slope of the dose-response curve and the extent and severity of the effect observed at LOAEL (and not toxicokinetic data). In the case of acute methanol poisoning in humans, the assessment factor is chosen with regard to the fact that dose-response and a 'non-toxic', tolerable dose (NOAEL) could not be established (i.e. although high number of methanol poisoning cases is described in open literature and in the reports from poison control centres, methanol dose is rarely known/stated and the database is rather limited) and severity of the effects - severe ocular toxicity and death (namely, lethal outcome is observed already at a dose level of 0.45 g/kg bw which is rather close to dose related to severe ocular toxicity of 0.26 g/kg bw, chosen as POD).

Conclusion: Using an assessment factor of 3, a **DNEL of 0.088 g/kg bw** is proposed by RAC.

Human health and environmental hazards of alternatives for methanol

The Dossier Submitter identified two alternative substances for methanol in windshield washing fluids (since products with a methanol concentration as low as proposed by the Dossier Submitter and RAC do not possess sufficient anti-freezing function, an adequate substitute for methanol needs to be added), namely ethanol and isopropanol (2-propanol) which are of lower toxicity compared to methanol. RAC recognised that other substances may also be used (e.g. ethylene glycol or propylene glycol in windshield washing fluids and *tert*-butyl alcohol in denatured alcohol) and these are further considered below.

Ethanol has a relatively low acute toxicity by all routes of exposure (Poisindex® Managements database).

Isopropanol also has a relatively low acute toxicity. It is irritating to the eyes, and at very high vapour concentrations also to the upper airways. Prolonged exposure may produce central nervous system depression and narcosis. The harmonised classification of 2-propanol according to the CLP Regulation (1272/2008) includes Eye Irrit. 2 H319; (Causes serious eye irritation), and STOT SE 3; H336 (May cause drowsiness or dizziness). It is not classified for environmental hazards according to the CLP Regulation.

Comparison of acute toxicity of ethanol and isopropanol with acute toxicity of methanol

According to the Poisindex® Managements database, a dose of 1 g/kg absolute ethanol (95% to 99% ethanol) is expected to cause mild to moderate intoxication in most adults,

[5] Guidance on information requirements and chemical safety assessment (Chapter R-8:Dose (concentration) - Response characterisation (Version 2.1))

and 5 to 6 g/kg is considered as potentially lethal in non-tolerant adult. A toxic oral dose of isopropanol is about 0.3 – 0.6 g/kg, and the probable oral lethal dose is approximately 3 g/kg bw (although as little as 1.3 g/kg bw was reported as fatal). Ethanol exposure is extremely common but *per se* rarely results in severe acute morbidity or death. However, ethanol abuse frequently precipitates traumatic injuries and, in chronic abusers, can lead to alcohol dependence (alcoholism) with severe health and social consequences. Severe poisoning cases with isopropanol may include haemorrhagic gastritis, hypotension, respiratory depression, and coma, but lethal outcome is rare and likely secondary to respiratory depression and aspiration.

On the other hand, a lethal oral methanol dose in the range as low as 0.45 – 0.51 g/kg bw has been reported (Bennett et al. 1953, Desai et al. 2013). Data from annual reports of the American Association of Poison Control Centers' National Data Poison Data System (NPDS) support the above statements regarding acute toxicity of studied alcohols showing 11 times higher incidence of major outcome and 54 times higher mortality among methanol exposure cases **compared to ethanol** exposure cases, during a 2-year period (Mowry et et al. 2012; Mowry et al. 2013). Incidence of a major outcome was 3.2 times higher and mortality 34 times higher among methanol exposure cases **compared to isopropanol** exposure cases, during the same period. Also, according to the Lithuanian National Health Insurance Fund under the Ministry of Health, data for a 2-year period (2013 and 2014) submitted during PC show 27 times higher mortality due to methanol **compared to ethanol** exposure (15% methanol-related mortality *vs.* 0.54% ethanol-related mortality).

The health effects of chronic abuse of ethanol are not considered here, because prevention of ethanol abuse is clearly not in the scope of proposed restriction. RAC is aware of the problem of chronic alcoholism in Europe but considers that the proposed methanol restriction is not expected to aggravate the issue, only prevent severe methanol poisonings, including lethal outcomes or cases with irreversible impairments such as blindness or brain damage.

RAC is aware that lowering methanol concentration in a product is not expected to make that product less attractive for alcohol abusers since methanol will have to be replaced by adequate alternatives, most frequently ethanol and/or isopropanol, which are also substances of abuse (especially ethanol). On the contrary, there is a concern that with an increase in the percentage of ethanol in windshield washing fluids, while eliminating the threat of concurrent methanol poisoning, these products will become more attractive to alcoholics. However, RAC does not consider that this potential increase in windshield washing fluids abuse will add significantly to the number of alcoholics or severity of their ethanol abuse. Namely, methanol-containing products (including windshield washing fluids as the most frequent cause of methanol poisonings in alcoholics according to data from several EU countries) are just a small portion of the total number of products containing non-consumable alcohol which are abused by alcoholics. According to data from annual reports of the American Association of Poison Control Centers' National Data Poison Data System (Mowry et al. 2013, Mowry et al. 2014), the number of cases of intentional exposure to non-consumable ethanol (hand sanitizers, mouthwash containing ethanol, ethanol-based rubbing alcohol, cleaning agents excluding automotive products and other non-beverage ethanol products without methanol or other toxic alcohol) was 27 times higher compared to the number of cases of intentional exposure to methanol-containing automotive products, including windshield washing fluids. Further, abuse of non-beverage alcohol presents only a small part of total alcohol abuse. For example, Estonian data showed that the age-standardized prevalence rate of non-beverage alcohol drinking was 1.4% among respondents who reported drinking at least once in their lifetime and were alcohol consumers at the time of the study (Pärna and Leon 2011). In Finland, a country with rather strict policies regarding consumable alcohol availability, national statistics indicate that consumption of non-beverage ethanol is below 1% of the total alcohol consumption (Karlsson et al. 2010; Varis and Virtanen 2015) (for further justification please refer to Background Document).

Regarding technical performance of these alternatives (ethanol and isopropanol), RAC

points out that they are both already in use in the EU in countries with very low winter temperatures (e.g. Norway).

Other alternatives recognised by RAC:

Propylene glycol (propane-1,2-diol) is not classified according to CLP, either for health or environmental hazards. According to ATSDR it is generally considered to be a safe chemical. The Food and Drug Administration (FDA) has classified propylene glycol as "*generally recognized as safe,*" and is acceptable for use in flavourings, drugs, and cosmetics, and as a direct food additive. According to the World Health Organization, the acceptable dietary intake of propylene glycol is 25 mg of propylene glycol for every kilogram (kg) of body weight. Propylene glycol is able to lower the freezing point of water, and is used, for example, as aircraft de-icing fluid. However, its demand as a substitute for methanol may be affected by its price (which is almost ten times higher than the price of methanol).

Ethylene glycol (ethane-1,2-diol), unlike the alternatives described above, could pose a significant health risk if used as an alternative to methanol. Although classified as Acute Tox. 4*; H302 (Harmful if swallowed), it has been frequently reported as a cause of severe poisonings in humans, including lethal outcomes (Ghannoum et al. 2014, Rogaczewska et al. 2014, Viinamäki et al. 2015). It metabolizes to glycolic and oxalic acid that cause metabolic acidosis and are mainly responsible for its toxic effects. It is more commonly used as an anti-freeze for engines than in windshield fluids (due to its corrosive properties, corrosion inhibitors have to be added to aqueous mixtures), but it could be found in some de-icing fluids for windshields (e.g. according to CICAD 2002, winter windshield washer fluids may contain ethylene glycol at up to 14% by weight). According to the ECHA database of registered chemicals, it is registered for “Use in/as de-icing/anti-icing applications/agents (Consumer use)” as Chemical product category PC 4: Anti-freeze and de-icing products. Its price is slightly higher (<10%) than the price of ethanol.

***tert*-butyl alcohol** (2-methylpropan-2-ol) is classified according to CLP as Acute Tox. 4* H225 (Harmful if inhaled) and STOT Single Exp. 3; H335 (May cause respiratory irritation). According to INCHEM/IPCS (1987), *tert*-butyl alcohol should be considered as a potential skin and eye irritant. At high concentrations, the vapour can cause narcosis, but there have been no reports of poisoning. *tert*-butyl alcohol (and isopropanol) were recommended by the Indirect Tax Expert Group (Draft Recommendation ITEG/R/2/2014) to be used in partial denaturation of alcohol in the manufacture of certain products (cosmetics, perfumes, hygiene products).

Conclusion: RAC acknowledges the substitutes identified by the Dossier Submitter (ethanol and isopropanol), and has named three other potential substitutes, namely propylene glycol, ethylene glycol and *tert*-butyl alcohol. Alternatives ethanol, isopropanol, propylene glycol and *tert*-butyl alcohol are of lower toxicity compared to methanol. In contrast, ethylene glycol can pose similar risks as methanol.

- Information on emissions and exposures

The Dossier Submitter limited the restriction proposal to two types of products, windshield washing fluids and denatured alcohol, since, according to the information obtained from Poison Control/Information Centres in Poland and Finland, these types of products represent the most common causes of severe poisonings with methanol-containing products.

Regarding the maximum amount of windshield washing fluid or denatured alcohol that is likely to be ingested over a 24-hour period, it is evident that up to 2 L of strong (distilled) spirits could be acutely ingested (Glazer & Dross 1993, Zakharov et al. 2014). Nevertheless, in the light of information contained in the Background Document (data from Polish Poison Control Centre) as well as in the majority of published case reports (Bennett et al. 1953, Scrimgeour 1980, Girault et al. 1999, Brahmi et al. 2007, Desai et al. 2013), RAC supports the Dossier Submitter proposal to consider the amount of 1 L (ingested over 24-hour period) as a realistic worst case scenario for intentional misuse.

RAC also agrees with the Dossier Submitter proposal for one exposure scenario for both windshield washing fluids and denatured alcohol, taking into account difficulties in the estimation of confounding effects of ethanol co-ingestion. It can be assumed that a higher percentage of ethanol in denatured alcohol compared to windshield washing fluid can affect the volume of ingested product (ingested volume of a product could be expected to decrease with an increase in ethanol content), as well as methanol toxicity due to ethanol-methanol interactions. RAC, however, is aware that the data on methanol and ethanol doses in reported cases of methanol poisoning in humans are too limited to allow quantitative assessment of methanol-ethanol interactions (Tables 1 and 2), and information on the pharmacokinetics of methanol in the presence of ethanol is scarce (Coulter et al. 2011; NIH 2007) (for further clarification please refer to Background Document).

Conclusion: RAC agrees with the Dossier Submitter to consider acute (over 24-hour period) ingestion of 1 L of windshield washing fluid or denatured alcohol as a realistic worst case scenario for intentional misuse, and to apply one exposure scenario for both product types.

- Characterisation of risk(s)

The Dossier Submitter performed their risk characterisation by calculating a dose of windshield washing fluids or denatured alcohol containing methanol which can result in death to humans, assuming lethal oral dose of methanol in humans of 0.3 g/kg bw (according to IPCS/WHO 1997), 70 kg bw, density of methanol of 0.792 g/ml (at 20 °C), and approximately 1L ingestion of methanol-containing product (as a maximal volume likely to be ingested). Based on these assumptions, the Dossier Submitter calculated that the methanol concentration in a product should be below 3% to prevent lethal poisoning with methanol.

Although for consumers a bw of 60 kg is normally used (according to ECHA Guidance), the Dossier Submitter considered 70 kg bw as more appropriate, based on the assumption that methanol-containing products are consumed mainly by adult men.

As noted above, RAC used a different POD, i.e. severe ocular toxicity instead of death,, which led to a DNEL of 0.088 g/kg bw. Also, 60 kg bw was used, according to ECHA Guidance. Namely, RAC is of the opinion that abuse of methanol-containing products cannot be assigned only to adult men, since female cases were also reported in the literature (Tables 1 and 2), and there is also the potential for abuse of methanol products during binge drinking in adolescents. Other assumptions were the same as proposed by the Dossier Submitter, namely, the density of methanol at 0.792 g/ml (at 20 °C) and ingestion of 1L of methanol-containing product as a realistic worst case scenario for intentional misuse.

Applying the formula:

$$\frac{\text{Consumer bw (60 kg)} \times \text{DNEL (0.088 g/kg bw)}}{\rho_{methanol}\ (0.792\ \text{g/ml}) \times 1000\ \text{ml}} \times 100 = \mathbf{0.67\%}$$

it was calculated that a critical limit of methanol concentration in a product is below 0.67% with RCR of 0.90 when rounded to 0.6%. Therefore, methanol concentration in a product <0.6% could be considered protective against methanol-induced severe ocular toxicity (as well as death).

Namely, if a 60 kg bw person within 24-hour period drinks 1 L of windshield washing fluid or denatured alcohol containing 0.6% of methanol, he/she will ingest 0.079 g/kg bw methanol, leading to an RCR of 0.90 (0.079 g/kg bw / 0.088 g/kg bw).

The population at the highest risk are chronic alcohol addicts who deliberately abuse

methanol-containing products as a cheap substitute for consumable alcohol. Non-alcoholics, however, can also be sporadically affected (e.g. binge drinking in adolescents, accidental ingestion).

The registration dossier advises that methanol concentration in liquid mixtures available for consumers should not exceed 2.5%. This limit, however, is intended to protect the general population from inhalation and dermal exposure to methanol in cleaning and de-icing agents, including windshield washing fluids, and is more than four times higher than 0.6% limit proposed by RAC.

- Evidence that the existing regulatory risk management instruments are not sufficient

Currently, no general EU-wide restriction of methanol or mixtures containing methanol is in force. Methanol or mixtures containing methanol are not included in Annex XVII (Restrictions on the manufacture, placing on the market and use of certain dangerous substances, mixtures and articles) of REACH Regulation. Furthermore, upon joining the EU, previous national legislation in many Member States was removed with a subsequent rise in numbers of deaths from poisoning (clearly seen e.g. in the Finnish data), however, some national legislation still remains (briefly reviewed below).

In Poland, due to significant numbers of methanol poisonings, the sale to consumers of methanol and mixtures containing methanol in concentrations equal to or higher than 3% (biofuels and fuels for sport motorboats and models are exempted) is restricted since 2014.

In certain other EU countries, namely in Sweden, Denmark, Norway, Lithuania, Germany and Austria, national legislation also restricts the sale of methanol and methanol-containing mixtures to the general public.

In Denmark, according to the Danish Statutory Order No 857 of 05/09/2009, methanol must not be used in engine coolants, in solutions used for preventing the freezing of carburetors or in de-icing fluids, such as washing fluid. Methanol content in products sold to the general public may not exceed 10% in Sweden, Denmark, Norway and Lithuania, and in Germany and Austria permission is needed to purchase products containing methanol at concentrations >10%. These restrictions are part of a national legislation which prohibits the selling of mixtures classified as acute toxic and labelled as “toxic” (T and T+) to the general public.

RAC agrees with the Dossier Submitter that a 10% limit value is clearly not protective enough to prevent severe methanol intoxication. A dose that could induce severely diminished visual acuity (vision reduced to finger-counting) is approximately 200 ml of a product containing 10% of methanol if 0.26 g/kg bw of ingested methanol is regarded as a minimal dose related to severe ocular toxicity in humans. Desai et al. (2013) reported 11% of patients with a lethal outcome and 36% with severe permanent visual damage after ingestion of illicit liquor containing 6.5% volume/volume methanol (in 40% ethanol).

According to CLP, the packaging of a substance or mixture containing methanol should be fitted with child-resistant fastenings if methanol is present in a concentration ≥3%. However, this measure is not expected to be efficient in adults.

Conclusion: RAC considers a 0.6% methanol concentration in the two proposed types of methanol-containing products to be protective against methanol-induced severe ocular toxicity and death. The calculation is based on consumer severe ocular toxicity as the POD leading to a DNEL of 0.088 g/kg bw, assuming a body weight of 60 kg and 1L ingestion of methanol-containing product in 24 hours as a realistic worst case scenario for intentional misuse.

In addition, RAC concludes that described regulatory risk management instruments at national level are not sufficient to control the risks of intentional misuse.

JUSTIFICATION THAT ACTION IS REQUIRED ON AN EU WIDE BASIS

Methanol-containing products caused poisoning among consumers (mostly alcohol addicts drinking winter windshield washing fluids and denatured alcohol as a surrogate for consumable alcohol) in several EU Member States, including Belgium, Bulgaria, Finland, Germany, Norway, Poland and the United Kingdom, with Poland, Finland and Bulgaria as the most severely affected (methanol poisoning has been recorded in other EU countries as well, but poisoning statistics data did not provide the source of the methanol, or the information was not submitted during PC). In Finland, for example, approximately 25 methanol-related deaths per year were recorded during the period 1996-2012, mostly caused by ingestion of windshield washing fluids.

In justification of an EU-wide restriction, the severity of the risk, namely death, severe ocular toxicity or other severe sequels to methanol poisoning, was also taken into account, as well as prevention of market distortion. The Dossier Submitter points out that methanol-containing products are widely used in all EU Member States and, given the significantly lower price of methanol compared to the price of alternatives (ethanol or isopropanol), restrictions limited to certain Member States would create a distortion of the market of methanol containing products.

It is also noted that several EU Member States have introduced certain legislative measures at national level to reduce the risk of methanol poisoning in general population, as presented in previous section.

Conclusion: RAC agrees with the Dossier Submitter that action is needed on an EU-wide basis, also taking into account severity of the risk, namely death, severe ocular toxicity or other severe sequels of methanol poisoning.

JUSTIFICATION THAT THE SUGGESTED RESTRICTION IS THE MOST APPROPRIATE EU WIDE MEASURE

Previous restrictions of methanol in Finland and Poland, regulated at national level, have proven to be effective in the reduction of the number of methanol poisonings in these countries. Nevertheless, as stated above, no general EU-wide restriction of methanol or mixtures containing methanol is currently in force. Legislative measures at national level in certain EU countries refer to methanol limits significantly above the limit proposed by RAC in this opinion (3% or 10% *vs.* 0.6%, respectively).

Besides REACH Annex XVII restriction proposal for methanol described in the Background Document, the Dossier Submitter did not identify any other EU legislation with the potential to reduce the identified risks.

Other management and enforcement options suggested during Public Consultation, such as the addition of bittering agents and social programs to tackle the issue of methanol-containing products abuse, are not considered to be adequate for the target population aimed to be covered with the proposed restriction (please refer to the Background Document for detailed justification).

During RAC consultation, minimum unit pricing for methanol was also suggested to be considered. However, information that would enable the evaluation of the effectiveness of this measure was not provided either by the Dossier Submitter or during Public Consultation, so minimum unit pricing for methanol was not further evaluated by RAC (it should be also noted that this measure is not in the remit of REACH).

Conclusion: RAC agrees with the Dossier Submitter that restriction of methanol is the most appropriate EU-wide measure.

Effectiveness in reducing the identified risks

Based on positive experience with national restrictions of methanol in Poland, and previously in Finland, the Dossier Submitter expects that an EU-wide methanol restriction will be effective in reducing the identified risks, namely severe methanol poisonings in consumers abusing methanol in windshield washing fluids and denatured alcohol as a cheap substitute for alcoholic beverages.

Poison Control Centres' statistics in Poland showed that the total number of poisonings with methanol was almost seven times lower during the period in which a ≤3% methanol restriction was in place (2001-2010) compared to the period without restriction (2011-2013). The number of fatal poisonings was eight times lower during the period with the restriction compared to time period without restriction[6]. New data for Poland, collected after the restriction was re-introduced (in January 2014), also shows a decrease in total number of methanol poisonings, although to a lesser degree, 2.7 times (230 cases in the winter 2012/2013 and the summer 2013 *vs.* 84 cases in the winter 2014/2015 and summer 2014). In Finland, data from the Poison Information Centre indicates eleven times lower incidence of fatal poisonings during a nine-year period in which a total ban of selling methanol-containing products to the general population was in place, compared to the 18-year period after this ban was lifted (according to data presented in the Background Document and Malinen 2003).

Conclusion: RAC agrees with the Dossier Submitter opinion on the expected effectiveness of the proposed restriction.

Practicality, including implementability, manageability and enforceability

➢ Implementability and manageability

The Dossier Submitter presented two alternatives for methanol in windshield washing fluids and denatured alcohol, ethanol and isopropanol, which are adequate and available, safer than methanol, and already in use. The implementation of the proposed restriction (by switching to alternative substances) is clear and understandable to all actors involved.

RAC agrees that the proposed restriction is implementable and manageable.

➢ Enforceability

RAC agrees with the Dossier Submitter and the Forum that the proposed restriction is enforceable through inspections, which may be done at the formulators' sites and in the retail sector as well.

The Forum expressed concern that the wording stated in the original proposal regarding methanol "as an additive to denatured alcohol" could be interpreted that denatured alcohol based on technical alcohol with no intentionally added methanol above the proposed methanol limit is not restricted, i.e. the supplier might claim that all methanol above 0.6% is not an additive but an impurity in technical alcohol. Therefore the Forum suggested considering the wording "*as a constituent of denatured alcohol*" instead of "*as an additive to denatured alcohol*". RAC agrees with the Forum, and suggests using the term 'component' instead of 'constituent' proposed by the Forum (justification is given on page 1 of the Opinion).

Monitorability

[6] The data for fatal poisonings are available for only one year with the restriction (2010) and three years without restriction (2011-2013)

RAC agrees with the Dossier Submitter and the Forum that due to the relevance of methanol as an impurity in alcohol-based food products and in the denaturation of technical alcohol-based products, various analytical methods exist for the determination of methanol in aqueous solutions of methanol and ethanol (e.g. EN 15721).

BASIS FOR THE OPINION

The Background Document, provided as a supportive document, gives the detailed grounds for the opinion.

Basis for the opinion of RAC

The main changes introduced in the restriction as suggested in this opinion compared to the restrictions proposed in the Annex XV restriction dossier submitted by Poland are:

1) In line with the Forum advice, the scope of the restriction proposal is changed in a way that windshield defrosters are added as a subtype of windshield washing fluids (for the justification supporting this change see BacD chapter A.1.2);
2) A DNEL value of 0.088 g/kg bw (based on minimal oral methanol dose leading to severe ocular toxicity, i.e. 0.26 g/kg bw with AF of 3) is proposed for the risk assessment (instead of 0.008 g/kg derived from an inhalatory OEL or the minimal acute oral lethal dose of 0.3 g/kg bw). Instead of 70 kg body weight used by the Dossier Submitter, 60 kg body weight was used in the calculation, as recommended in ECHA Guidance. Thus, the methanol limit value for windshield washing fluids and denatured alcohol is lowered from the value proposed by the Dossier Submitter of ≥3% to **≥0.6 %;**
3) Other alternatives not mentioned in the Background Document, but recognised by RAC, are discussed.

References (additional to those cited in the Background Document)

Bennett IL Jr, Cary FH, Mitchell GL Jr, Cooper MN. Acute methyl alcohol poisoning: a review based on experiences in an outbreak of 323 cases. Medicine (Baltimore). 1953;32:431-63.

Brahmi N, Blel Y, Abidi N, Kouraichi N, Thabet H, Hedhili A, Amamou M. Methanol poisoning in Tunisia: report of 16 cases. Clin Toxicol (Phila). 2007;45:717-20.

CICAD - Concise International Chemical Assessment Document 45. Ethylene glycol: human health aspects. WHO, Geneva 2002

Coulter CV, Isbister GK, Duffull SB. The pharmacokinetics of methanol in the presence of ethanol: a case study. Clin Pharmacokinet 2011;50:245-51.

Desai T, Sudhalkar A, Vyas U, Khamar B. Methanol poisoning: predictors of visual outcomes. JAMA Ophthalmol. 2013;131:358-64.

Duke-Elder WS. Textbook of Ophtalmology, Vol III. St. Louis, CV, Mosby Co, 1945 (not available)

Erlanson P, Fritz H, Hagstam KE, Liljenberg B, Tryding N, Voigt G. Severe methanol intoxication. Acta Med Scand 1965;177:393-408.

FIOH. Development of Initial REACH Exposure Scenarios for Methanol. Search Results. Finnish Institute of Occupational Health, Helsinki 2008 (Translation 2009)

Fujihara M, Kikuchi M, Kurimoto Y. Methanol-induced retinal toxicity patient examined by optical coherence tomography. Jpn J Ophthalmol 2006;50:239-41.

Ghannoum M, Hoffman RS, Mowry JB, Lavergne V. Trends in toxic alcohol exposures in the United States from 2000 to 2013: a focus on the use of antidotes and extracorporeal treatments. Semin Dial. 2014;27:395-401.

Girault C, Tamion F, Moritz F, Callonnec F, Droy JM, Bonmarchand G, Leroy J. Fomepizole (4-methylpyrazole) in fatal methanol poisoning with early CT scan cerebral lesions. J Toxicol Clin Toxicol. 1999;37:777-80.

Glazer M, Dross P. Necrosis of the putamen caused by methanol intoxication: MR findings. AJR Am J Roentgenol 1993;160:1105-6.

Gonda A, Gault H, Churchill D, Hollomby D. Hemodialysis for methanol intoxication. Am J Med. 1978;64:749-58.

IPCS, ENVIRONMENTAL HEALTH CRITERIA 196, Methanol. WHO, Geneva 1997

IPCS, Poisons Information Monograph 335, Methanol. WHO, Update 2001

Jongeneelen FJ, Berge WF. PBTK-model IndusChemFate, version 2.00 - User manual 2

Jongeneelen FJ, Berge WF. A generic, cross-chemical predictive PBTK model with multiple entry routes running as application in MS Excel; design of the model and comparison of predictions with experimental results. Ann Occup Hyg 2011;55(8):841-64

Karlsson T et al. A new alcohol environment. Trends in alcohol consumption, harms and policy: Finland 1990 – 2010, Research report. Nordic Studies on Alcohol and Drugs 2010, Vol 27:497-513

Malinen A. Survey of the Use of Alcohol Surrogates in Finland Year 2002. Helsinki 2003

Martensson E, Olofsson U, Heath A. Clinical and metabolic features of ethanol-methanol poisoning in chronic alcoholics. The Lancet 1988:1(8581):327-28

Massoumi G, Saberi K, Eizadi-Mood N, Shamsi M, Alavi M, Morteza A. Methanol poisoning in Iran, from 2000 to 2009. Drug Chem Toxicol. 2012;35:330-3.

Methanol REACH Consortium Technical Committee Working Document: Points of Departure for Acute Methanol Toxicity by Ingestion, September 2015

Moschos MM, Gouliopoulos NS, Rouvas A, Ladas I. Vision loss after accidental methanol intoxication: a case report. BMC Res Notes 2013;6:479.

Mowry JB, Spyker DA, Cantilena LR Jr, Bailey JE, Ford M. 2012 annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 30th Annual Report. Clin Toxicol 2013;51:949–1229

Mowry JB, Spyker DA, Cantilena LR Jr, McMillan N, Ford M. 2013 annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 31st Annual Report. Clin Toxicol 2014;52:1032–83

NIH National Institute on Alcohol Abuse and Alcoholism. Alcohol metabolism: an update. NIH, Rockville, MD: 2007

Pärna K, Leon DA. Surrogate alcohol drinking in Estonia. Alcohol Clin Exp Res 2011;35:1454-7

Poisindex® Managements database (Truven Health Analytics Inc. MICROMEDEX® Healthcare Series Vol. 165, 2015

Rogaczewska A, Kobza-Sindlewska K, Krakowiak A, Piekarska-Wijatkowska A. [Acute alcohol poisonings among patients in Toxicology Unit, Nofer Institute of Occupational Medicine in the period of time 2007-2012] [Article in Polish]. Przegl Lek. 2014;71:479-83.

Röe O. The metabolism and toxicity of methanol. Pharmacol Rev 1955;7: 399-412. (not available)

Scrimgeour EM. Outbreak of methanol and isopropanol poisoning in New Britain, Papua New Guinea. Med J Aust 1980;2:36-8.

Varis T, Virtanen S. Alcoholic beverage consumption 2014. National Institute for Health and Welfare: Official Statistics of Finland 14/2015

Viinamäki J, Sajantila A, Ojanperä I. Ethylene Glycol and Metabolite Concentrations in Fatal Ethylene Glycol Poisonings. J Anal Toxicol. 2015;39:481-5.

Wood CA, Buller F. Poisoning by wood alcohol. JAMA 1904;43:972, 1058, 1117, 1213, 1289.

Zakharov S, Pelclova D, Urban P et al. Czech mass methanol outbreak 2012: epidemiology, challenges and clinical features. Clin Toxicol (Phila) 2014;52:1013-24.

Ziegler SL. The ocular menace of wood alcohol poisoning. British Journal of Opthalmology 1921;5:365-73