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Questions and answers on benzyl alcohol used as an excipient in medicinal products for human use

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This document should be read in the context of the revision of the Annex of the European Commission guideline 'Excipients in the labelling and package leaflet of medicinal products for human use' (EMA/CHMP/302620/2017) [1].

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1. What is benzyl alcohol and why is it used as an excipient?

Benzyl alcohol is an aromatic alcohol with the formula C_7H_8O. In the body, benzyl alcohol is metabolised into benzoic acid (for more information on benzoic acid see the dedicated questions and answers document [9]).

It is used as an excipient for its preservative properties, as a solubilising agent or as a fragrance[1] (cutaneous use).

Other use as active ingredient in antiseptic and local anaesthetic products will not be discussed in this document (not in the scope).

2. Which medicinal products contain benzyl alcohol?

Benzyl alcohol is mainly used as an excipient in medicinal products that are administered intramuscularly, such as antibiotics, anti-inflammatory or antipsychotic medicines where its anaesthetic properties reduce pain at the injection site. Benzyl alcohol is also present in medicinal products administered intravenously (anti-cancer drugs, heparins, cardiovascular drugs). Finally, benzyl alcohol is used as a preservative in many topical preparations, such as antifungal and anti-inflammatory products.

3. What are the safety concerns?

The main problem associated with the use of benzyl alcohol is the risk of accumulation in newborn babies (pre-and full-term) due to metabolic immaturity. Benzyl alcohol administered intravenously in the range of 100 to 200 mg/kg/day has been linked to the “gasping syndrome” in several pre-term newborns with metabolic acidosis that resulted in deterioration of the neurological status, cardio-vascular failure and haematological anomalies [3, 6]. This syndrome is associated with the accumulation of benzyl alcohol and the majority of poisonings were fatal.

There are no animal toxicological data for parenteral or topical use of benzyl alcohol. However, oral absorption is close to 100%, hence recommendations for oral use are considered applicable for other routes of administration. Regarding oral juvenile studies, only one short-term study has been performed in juvenile rats [5], which established a NOAEL of 300 mg/kg/day which is close to the adult. There are no juvenile animal toxicity studies related to long-term use.

Based on animal toxicity data, the SFC (Scientific Committee on Food) of the European Commission, has reviewed the data on benzyl alcohol in 2002 [10] and has added benzyl alcohol to the ADI group of 0-5 mg/kg bw. This position was based on a previous position given by EPA (the US Environmental Agency) in 1989 [4]. The EPA’s review relied on toxicology studies performed by the NTP published in 1989 [8]. In 2002 the Scientific Committee on Food (SCF) has reviewed the data on benzyl alcohol in 2002. The SCF confirmed the inclusion of benzyl alcohol in the group ADI of 0–5 mg/kg for benzoic acid and benzoates, as agreed in its previous opinion of 1981. Young children (< 3 years old) may not be sufficiently mature to metabolize and eliminate benzyl alcohol as efficiently as adults. Therefore the upper limit of the ADI should be considered with caution in this age group [10].

[1] See also ‘Information for the package leaflet for fragrances containing allergens used as excipients in medicinal products for human use’ (EMA/CHMP/273718/2014).

4. What are the reasons for updating the information in the package leaflet?

The recommendations in the 2003 guideline are incomplete and too strict (see annex 1). While this excipient should not be used in neonates, it may be used for children aged older than 4 weeks with caution. In addition, the thresholds needed to be revised.

5. Proposal for an updated information in the package leaflet

Name	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Benzyl alcohol	All routes of administration	Zero	This medicine contains x mg benzyl alcohol in each <dosage unit><unit volume> <which is equivalent to x mg/<weight><volume>>. Benzyl alcohol may cause allergic reactions.	
	Oral, parenteral	Zero	Benzyl alcohol has been linked with the risk of severe side effects including breathing problems (called “gasping syndrome”) in young children. Do not give to your newborn baby (up to 4 weeks old), unless recommended by your doctor.	Intravenous administration of benzyl alcohol has been associated with serious adverse events and death in neonates (“gasping syndrome”). The minimum amount of benzyl alcohol at which toxicity may occur is not known. Warning in section 4.4 in the SmPC should be given if used in neonates.
			Do not use for more than a week in young children (less than 3 years old), unless advised by your doctor or pharmacist.	Increased risk due to accumulation in young children.
			Ask your doctor or pharmacist for advice if you are pregnant or breast feeding. This is because large amounts of benzyl alcohol can build-up in your body and may cause side effects (called “metabolic acidosis”).	

Name	Route of Administration	Threshold	Information for the Package Leaflet	Comments
			Ask your doctor or pharmacist for advice if you have a liver or kidney disease. This is because large amounts of benzyl alcohol can build-up in your body and may cause side effects (called “metabolic acidosis”).	High volumes should be used with caution and only if necessary, especially in subjects with liver or kidney impairment because of the risk of accumulation and toxicity (metabolic acidosis).
	Topical	Zero	Benzyl alcohol may cause mild local irritation.	

Further scientific background is available in the report entitled ‘Benzyl alcohol and benzoic acid group used as excipients’ [2].

References

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8. NTP (National Toxicology Program), Technical report on the toxicology and carcinogenesis studies of benzyl alcohol (CAS No. 100-51-6) in F344/n rats and B6C3F1 mice (gavage studies), 1989.
9. Questions and answers on benzoic acid and benzoates used as excipients in medicinal products for human use (EMA/CHMP/508188/2013).
10. SCF (Scientific Committee on Food) 2002, Opinion of the Scientific Committee on Food on Benzyl alcohol, 2002. Available at: http://ec.europa.eu/food/fs/sc/scf/out138_en.pdf

Annex 1 - Information in the package leaflet as per 2003 Guideline [7]

Name	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Benzyl alcohol	Parenteral	Exposures less than 90 mg/kg/day	Must not be given to premature babies or neonates. May cause toxic reactions and allergic reactions in infants and children up to 3 years old.	SPC: 'allergic' should be expressed as 'anaphylactoid' The amount of benzyl alcohol in mg per <volume> should be stated in the package leaflet and SPC.
		90 mg/kg/day	Must not be given to premature babies or neonates. Due to the risk of fatal toxic reactions arising from exposure to benzyl alcohol in excess of 90 mg/kg/day, this product should not be used in infants and children up to 3 years old.	The amount of benzyl alcohol per <volume> should be stated in the package leaflet and SPC.