# Szükséges-e nagyobb figyelmet szentelnünk a segédanyagoknak?

## - gyógyszerek és tápszerek segédanyagai, mint potenciális allergének

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*Kép forrása: https://www.expresspharma.in/gattefosse-launches-three-new-pharmaceutical-excipients/*

# Segédanyag fogalma

- Segédanyag a gyógyszernek a hatóanyagtól és a csomagolóanyagtól eltérő bármely összetevője (2005. évi XCV. törvény -Gyógyszer tv.)

- Segédanyagnak nevezünk -a hatóanyag(ok)on kívül- minden olyan összetevőt, amelyet a gyógyszerkészítmény tartalmaz vagy amelyet előállításához felhasználtak. A segédanyag lehet: a hatóanyag hordozója (vivőanyag vagy készítményalap) vagy a hordozó egyik összetevője, és alkalmazhatják azzal a céllal, hogy befolyásolja a termék **stabilitás**át, **biofarmáciai profil**ját, **küllem**ét és **felhasználhatós**ágát a beteg számára, továbbá megkönnyítse a termék **előállítás**át. Egy gyógyszerkészítmény általában többféle segédanyagot tartalmaz (Ph. Hg. VIII.)

# Segédanyag alkalmazásával összefüggő kockázatok

- Több ezer segédanyag, sokszor 10 fajta egy gyógyszerkészítményben
- Segédanyagot tartalmazó gyógyszer terápiás területe, gyermekgyógyászati alkalmazás, generikumok
- Segédanyag aránya, mennyisége (napi max. dózisban)
- Segédanyaggal szembeni intolerancia, mellékhatások, túlérzékenység, toxicitás
- Segédanyaggal bevitt szennyezettség (pl. mikrobiológiai, gyártásból származó komponensek, keresztszennyeződések)
- Hamisított segédanyagok
- Új segédanyagok iránti igények, multifunkcionális segédanyagok, korlátozott biztonsági adatok

# Leggyakrabban problémát okozó segédanyagok

- Aszpartám
- Azofestékek
- Benzalkónium-klorid
- Benzoesav / benzoátok
- **Benzil-alkohol**
- **Bórsav /borátok**
- Búzakeményítő (glutén)
- **Ciklodextrinek**
- Dextránok
- **Etanol**
- Fenilalanin
- Foszfátok
- Fruktóz, galaktóz, szorbit
- Glicerin
- Gyapjúviasz (lanolin)
- Illatanyagok
- Karboxi-metil-cellulóz
- Laktóz
- **Makrogolok (polietilén-glikol)**
- Mogyoróolaj
- Nátrium-lauril-szulfát
- Parahidroxibenzoátok
- Perubalzsam
- Poliszorbátok (PS 80, PS 20)
- Povidon
- Prolin
- **Propilén-glikol**
- Szerves higanyvegyületek
- Szezámolaj
- Szójaolaj
- Xilit
- Zselatin

# Benzil-alkohol

| | | | | | |
|---|---|---|---|---|---|
| **Benzyl alcohol** | **09/10/2017** | Oral, parenteral | Zero | Benzyl alcohol has been linked with the risk of severe side effects including breathing problems (called "gasping syndrome") in young children.<br><br>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.<br><br>Warning in section 4.4 in the SmPC should be given if used in neonates. |
| **Benzyl alcohol** | **09/10/2017** | Oral, parenteral | Zero | 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. |
| **Benzyl alcohol** | **09/10/2017** | Oral, parenteral | Zero | 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"). | |
| **Benzyl alcohol** | **09/10/2017** | Oral, parenteral | Zero | 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). |
| **Benzyl alcohol** | **09/10/2017** | Topical | Zero | Benzyl alcohol may cause mild local irritation. | |

Felh.: tartósító tulajdonságai miatt segédanyagként, oldódást elősegítő anyagként
*(pl.: Clindamycin inj., Cordarone inj., Diazepam desitin, Heparibene Na inj., Synacthen depot inj., Ferrlecit inj.)*



Forrás: https://www.ema.europa.eu/

# Etanol

| | | | | | | |
|---|---|---|---|---|---|---|
| **Ethanol** | **22/11/2019** | Oral<br>Parenteral<br>Inhalation | 15 mg/kg per dose | This medicine contains x mg of alcohol (ethanol) in each <dosage unit><unit volume> <which is equivalent to x mg/<weight><volume>><(y% w/<w><v>)>. The amount in <dose><volume> of this medicine is equivalent to A ml beer or B ml wine.<br><br>The amount of alcohol in this medicine is not likely to have an effect in adults and adolescents, and its effects in children are not likely to be noticeable. It may have some effects in younger children, for example feeling sleepy.<br><br>The alcohol in this medicine may alter the effects of other medicines. Talk to your doctor or pharmacist if you are taking other medicines.<br><br>If you are pregnant or breast-feeding, talk to your doctor or pharmacist before taking this medicine.<br><br>If you are addicted to alcohol, talk to your doctor or pharmacist before taking this medicine. | To calculate the equivalent volume of beer and wine, assume the ethanol content of beer to be 5% v/v (alcohol by volume, ABV), which is equivalent to 4% w/v, and of wine to be 12.5% v/v or 10% w/v (the specific gravity of ethanol has been approximated as 0.8).<br><br>Where relevant, the interactions of ethanol should be stated in the SmPC (section 4.5).<br><br>Suggestion for information in the SmPC:<br>A dose of (select maximum dose) of this medicine administered to (a child A years of age and weighing B kg or an adult weighing 70 kg) would result in exposure to C mg/kg of ethanol which may cause a rise in blood alcohol concentration (BAC) of about D mg/100 ml (see Appendix 1 of report EMA/CHMP/43486/2018).<br><br>For comparison, for an adult drinking a glass of wine or 500 ml of beer, the BAC is likely to be about 50 mg/100 ml.<br><br>Co-administration with medicines containing e.g. propylene glycol or ethanol may lead to accumulation of ethanol and induce adverse effects, in particular in young children with low or immature metabolic capacity.<br><br>When a dose is given over prolonged period (e.g. by slow infusion over several hours), the rise in BAC will be less and the effects of ethanol may be |

Felh.: oldószerként a gyógyszer oldhatóságának javítására, extrakciós oldószerként gyógynövénykészítményekben, bakteriosztatikus, baktericid, gombaölő és virucid hatású *(pl.: Bactrimel / Cotrim inj., Epanutin inj., Prostin inj., Simdax inj.)*



Forrás: https://www.ema.europa.eu/

# Propilén-glikol

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| **Propylene glycol (E 1520) and esters of propylene glycol** | **09/10/2017** | All | 1 mg/kg/day | This medicine contains x mg propylene glycol in each <dosage unit><unit volume> <which is equivalent to x mg/<weight><volume>>. | |
| **Propylene glycol (E 1520) and esters of propylene glycol** | **09/10/2017** | Oral, parenteral | 1 mg/kg/day | If your baby is less than 4 weeks old, talk to your doctor or pharmacist before giving them this medicine, in particular if the baby is given other medicines that contain propylene glycol or alcohol. | Co-administration with any substrate for alcohol dehydrogenase such as ethanol may induce serious adverse effects in neonates. |
| **Propylene glycol (E 1520) and esters of propylene glycol** | **09/10/2017** | Oral, parenteral | 50 mg/kg/day | If your child is less than 5 years old, talk to your doctor or pharmacist before giving them this medicine, in particular if they use other medicines that contain propylene glycol or alcohol. | Co-administration with any substrate for alcohol dehydrogenase such as ethanol may induce adverse effects in children less than 5 years old. |
| **Propylene glycol (E 1520) and esters of propylene glycol** | **09/10/2017** | Oral, parenteral | 50 mg/kg/day | If you are pregnant or breast-feeding, do not take this medicine unless recommended by your doctor. Your doctor may carry out extra checks while you are taking this medicine. | While propylene glycol has not been shown to cause reproductive or developmental toxicity in animals or humans, it may reach the foetus and was found in milk. As a consequence, administration of propylene glycol to pregnant or lactating patients should be considered on a case by case basis. |
| **Propylene glycol (E 1520) and esters of propylene glycol** | **09/10/2017** | Oral, parenteral | 50 mg/kg/day | If you suffer from a liver or kidney disease, do not take this medicine unless recommended by your doctor. Your doctor may carry out extra checks while you are taking this medicine. | Medical monitoring is required in patients with impaired renal or hepatic functions because various adverse events attributed to propylene glycol have been reported such as renal dysfunction (acute tubular necrosis), acute renal failure and liver dysfunction. |

Felh.:bőrgyógyászati készítményekben nedvesítőszerként, oldatokban tartósítószerként, aeroszolokban parenterális készítményekben és oldatokban segédoldószerként *(pl.: Dexamethason-ratiopharm inj., Bactrimel inj., Epanutin inj.)*



Forrás: https://www.ema.europa.eu/

# Ciklodextrin

| | | | | | |
|---|---|---|---|---|---|
| **Cyclodextrins**<br><br>e.g.:<br>Alfadex<br>Betadex (E 459)<br>γ-cyclodextrin<br>Sulfobutyl-ether-β-cyclodextrin (SBE-β-CD)<br>Hydroxypropyl betadex<br>Randomly methylated β-cyclodextrin (RM-β-CD) | **09/10/2017** | All | 20 mg/kg/day | This medicine contains x mg cyclodextrin(s) in each <dosage unit><unit volume> <which is equivalent to x mg/<weight><volume>>.<br><br>Do not use in children less than 2 years old unless recommended by your doctor. | Cyclodextrins (CDs) are excipients which can influence the properties (such as toxicity or skin penetration) of the active substance and other medicines. Safety aspects of CDs have been considered during the development and safety assessment of the drug product, and are clearly stated in the SmPC.<br><br>There is insufficient information on the effects of CDs in children < 2 years old. Therefore, a case by case judgement should be made regarding the risk/benefit for the patient.<br><br>Based on animal studies and human experience, harmful effects of CDs are not to be expected at doses below 20 mg/kg/day. |
| **Cyclodextrins**<br><br>e.g.:<br>Alfadex<br>Betadex (E 459)<br>γ-cyclodextrin<br>Sulfobutyl-ether-β-cyclodextrin (SBE-β-CD)<br>Hydroxypropyl betadex<br>Randomly methylated β-cyclodextrin (RM-β-CD) | **09/10/2017** | Oral | 200 mg/kg/day | Cyclodextrins may cause digestive problems such as diarrhoea. | At high doses cyclodextrins can cause reversible diarrhoea and cecal enlargement in animals. |
| **Cyclodextrins**<br><br>e.g.:<br>Alfadex<br>Betadex (E 459)<br>γ-cyclodextrin<br>Sulfobutyl-ether-β-cyclodextrin (SBE-β-CD)<br>Hydroxypropyl betadex<br>Randomly methylated β-cyclodextrin (RM-β-CD) | **09/10/2017** | Parenteral | 200 mg/kg/day and use for > 2 weeks | If you have a kidney disease, talk to your doctor before you receive this medicine. | In children less than 2 years, the lower glomerular function may protect against renal toxicity, but can lead to higher blood levels of cyclodextrins.<br><br>In patients with moderate to severe renal dysfunction accumulation of cyclodextrins may occur. |

Felh: vízoldékonyság fokozására, gyógyszerek biológiai hozzáférhetőségének javítására tablettákban, parenterális oldatokban, orrsprayben és szemcseppekben

*(pl.: Vorikonazol inf., Veklury inf., sugammadex, Flector Rapiven inj.)*



Forrás: https://www.ema.europa.eu/

# Bórsav / borát

| Name | Route of Administration | Threshold | Information for the Package Leaflet | Comments |
|---|---|---|---|---|
| **Boric acid (and borates)** | All routes of administration | 1 mg B/day* | Do not give to a child less than 2 years old as this medicine contains boron and may impair fertility in the future. | * 1 mg B (Boron) = 5.7 mg boric acid<br>See Q&A document [link to be inserted] for further calculations.<br>Amount of boron per age group which may impair fertility if exceeded:<br>Age / Safety limit<br>< 2 years / 1mg B/day<br>< 12 years / 3 mg B/day<br>< 18 years** / 7 mg B/day<br>≥ 18 years** / 10 mg B/day<br>** This amount may also cause harm to the unborn child. |
| | | 3 mg B/day* | Do not give to a child less than 12 years old as this medicine contains boron and may impair fertility in the future. | |
| | | 7 mg B/day* | Do not give to a child less than 18 years old as this medicine contains boron and may impair fertility in the future.<br>If you are pregnant, talk to your doctor before taking this medicine as it contains boron which may be harmful to your baby. | |

Further scientific background is available in the report entitled 'Boric acid and borates used as excipients' [3].

Felh.: antimikrobiális tartósítószer, pufferanyag a pH szabályozására.
*Elsősorban magisztrális készítményekben, szemcseppekben*



Forrás: https://www.ema.europa.eu/

# Élelmiszerekből előállított segédanyagok

- Tojás (tojás fehérje, ovalbumin, lecitin, foszfolipidek)
  - influenza vakcina, probiotikumok, propofol, zsíremulziók, TPN
- Hal
  - Protamin -inzulinok, halolaj, multivitaminok
- Zselatin
  - Lágy zselatin kapszulák, plazma expanderek, varicella vakcina, vérzéscsillapító szivacs
- Tej (kazein, tejfehérje, laktóz)
  - probiotikumok, tabletták, kapszulák, porok, inhalációs készítmények
- Mogyoróolaj
  - dimercaptol inj.
- Szezámolaj
  - Haloperidol decanoat inj
- Szójaolaj
  - propofol, progeszteron kapsz., liposzómás amphotericin B
- Kagyló (glükózamin)
- Búzakeményítő (glutén)


ISOPRINOSINE 500 MG TABLETTA - LAKTÓZ, BÚZAKEMÉNYÍTŐ, BENZOÁT TARTALOM

| Megnevezés | Tartalom | Mennyiség |
|---|---|---|
| Laktóz | Nincs | |
| Búzakeményítő | Van | |
| Benzoát | Nincs | |

# Segédanyag szennyeződés




**Table 1**
Summary major diethylene glycol mass poisoning incidences.

| Outbreak Year | Outbreak Country | Implicated Medication | Route of Exposure | Reference |
|---|---|---|---|---|
| 1937 | USA | Elixir of Sulfanilamide | oral | Calvery and Klumpp (1939) |
| 1969 | South Africa | Sedative | oral | Bowie and McKenzie (1972) |
| 1986 | India | Glycerin | unknown | |
| 1990 | Nigeria | Acetaminophen | oral | |
| 1990 | Bangladesh | Acetaminophen | oral | |
| 1992 | Argentina | Propolis syrup | oral | |
| 1995 | Haiti | Acetaminophen | oral | |
| 1998 | India | Cough expectorant | oral | |
| 1998 | India | Acetaminophen | oral | |
| 2006 | Panama | Cough syrup | oral | |
| 2008 | Nigeria | Analgesic | oral | |

Adapted from Sosa et al. (2014).

World Health Organization

Health Topics ▾ Countries ▾ Newsroom ▾ Emergencies ▾

Home / Disease Outbreak News / Item / Melamine-contaminated powdered infant formula in China - update 2

## 2008 - China

29 September 2008

*29 September 2008* - More than 54,000 infants and young children have sought medical treatment in relation to the melamine-contaminated dairy products in China, causing kidney stone. Three deaths among infants have been confirmed, more than 13,000 infants are in hospital. Kidney stones in infants are normally very rare.

The World Health Organization has published *"Melamine and Cyanuric acid: Toxicity, Preliminary Risk Assessment and Guidance on Levels in Food"*. This preliminary guidance was developed to assist national authorities in the decision-making process on deciding possible health concern of melamine levels in food.

This preliminary guidance is proposed as a first pragmatic approach until more data become available which would allow a more detailed assessment.


World Health Organization

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Home / News / Medical Product Alert N°6/2022: Substandard (contaminated) paediatric medicines

## Medical Product Alert N°6/2022: Substandard (contaminated) paediatric medicines

### Substandard (contaminated) paediatric medicines identified in WHO region of Africa

5 October 2022 | Medical product alert | Geneva | Reading time: 2 min (455 words)

**Alert Summary**

This WHO Medical Product Alert refers to four substandard products, identified in The Gambia and reported to WHO in September 2022. Substandard medical products are products that fail to meet either their quality standards or specifications and are, therefore "out of specification"[1].

The four products are *Promethazine Oral Solution, Kofexmalin Baby Cough Syrup, Makoff Baby Cough Syrup* and *Magrip N Cold Syrup*. The stated manufacturer of these products is Maiden Pharmaceuticals Limited (Haryana, ... The stated manufacturer has not provided guarantees to WHO on the safety and quality of these ...

...sis of samples of each of the four products confirms that they contain unacceptable amounts of ... and ethylene glycol as contaminants. To date, these four products have been identified in The ... have been distributed, through informal markets, to other countries or regions.

...ons: https://www.who.int/teams/regulation-prequalification/incidents-and-SF/background/definitions

...ol and ethylene glycol are toxic to humans when consumed and can prove fatal

...include abdominal pain, vomiting, diarrhoea, inability to pass urine, headache, altered mental state, ... injury which may lead to death.

...ese products should be considered unsafe until they can be analyzed by the relevant National ...orities.

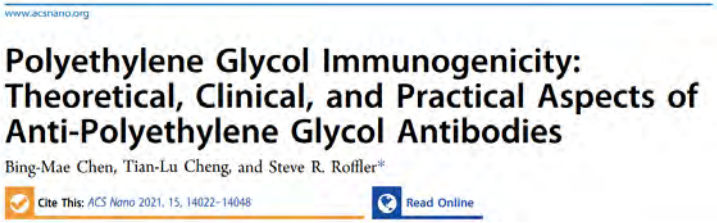
... products referenced in this alert are unsafe and their use, especially in children, may result in ... death.

...ulatory authorities and the public

... detect and remove these substandard products from circulation to prevent harm to patients.

...ncreased surveillance and diligence within the supply chains of countries and regions likely to be ... products. Increased surveillance of the informal/unregulated market is also advised.

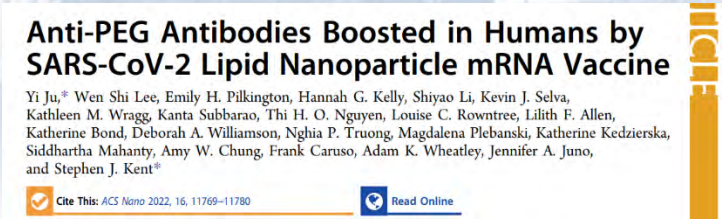
# Esetismertetés -anti-PEG Abs




- 2016. 6 éves kisfiú -haemophilia diagnózis, VIII-as faktor szubsztitúció
- 2020-tól rendszeres faktorpótlás, pk alapján megfelelő faktorszint
- 2021.07.19. hosszított felezési idejű készítményre váltás → PEG-al konjugált VIII-as faktor →tesztdózis utáni pk mérés nem megfelelő faktorszintet mutatott
- PEG ellenes antitestek kimutatása (készítmény elleni neutralizáló AT jelenléte kizárható)
- 2021.08.23. PEG –et nem tartalmazó faktor készítmény beállítása után megfelelő faktorszint

*2021.07.08. COVID-19 mRNS-vakcina*

- anti-PEG antitestek → felgyorsult gyógyszerkiürülés, csökkent klinikai hatékonyság, súlyos túlérzékenységi reakciók.
- SARS-CoV-2 RNS vakcinák széles körben elterjedt alkalmazása, gyakori emlékeztető oltások hatása



# Segédanyag alkalmazásával összefüggő kockázatok csökkentésének lehetőségei


- Gyógyszermellékhatás, hatáscsökkenés → gondoljunk a segédanyagokra is
- Segédanyag toxicitás, allergia megelőzése, felismerése

**klinikai gyógyszerész szerepe**

  - gyógyszer összetételének pontos ismerete, gyógyszeres anamnézis, 9M, off-label indikációk

- *Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' (SANTE-2017-11668)*
- *European Paediatric Formulation Initiative (EuPFI) - STEP (Safety and Toxicity of Excipients for Paediatrics) adatbázis*

  *Pediatric Excipient Risk Assessment (PERA)*
- *Az Európai Parlament és Tanács 2001/83/EK irányelve (2001. november 6.) az emberi felhasználásra szánt gyógyszerek közösségi kódexéről*