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Risk assessment of neonatal excipient exposure: Lessons from food safety and other areas☆,☆☆

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ABSTRACT

Newborn babies can require significant amounts of medication containing excipients intended to improve the drug formulation. Most medicines given to neonates have been developed for adults or older children and contain excipients thought to be safe in these age groups. Many excipients have been used widely in neonates without obvious adverse effects. Some excipients may be toxic in high amounts in which case they need careful risk assessment. Alternatively, it is conceivable that ill-founded fears about excipients mean that potentially useful medicines are not made available to newborn babies. Choices about excipient exposure can occur at several stages throughout the lifecycle of a medicine, from product development through to clinical use. Making these choices requires a scalable approach to analysing the overall risk. In this contribution we examine these issues.

Contents

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1. Introduction

Excipients have been defined in various ways. For example, the International Pharmaceutical Excipients Council (IPEC) defines an excipient "as any substance other than the active drug or pro-drug that is included in the manufacturing process or is contained in a finished pharmaceutical dosage form" [1]. The same organisation suggests a more nuanced definition: "Substances other than the active pharmaceutical ingredient (API) which have been appropriately evaluated for safety and are intentionally included in a drug delivery system" [2]. The difference between the definitions reflects different perspectives on the manufacture and supply of medicines. We favour the first definition since it includes all steps of the manufacturing process and at present many excipients have not been appropriately evaluated for safety in neonates.

Excipients are found in many medicines given to neonates [3–6]. In some cases this is necessary as it would otherwise be impossible to formulate the active ingredient without them. Excipients may also be helpful because preservatives or other agents added can enable a product to become commercially viable and market-worthy. The varied pharmaceutical function of certain excipients means that choices regarding their inclusion within a formulation have to be made early in the product development process.

Excipients have been given to many millions of neonates with very few clear-cut cases of harm. When harm has been reported it often associated with higher amounts of excipients than are usually used [7–9]. Nevertheless, there is a need to consider the potential for harm, particularly if there is evidence that a particular excipient may cause problems in the developing organism. There is a significant amount of information available to date about excipients, some of which is relevant to neonates. This can be used to identify minimal-risk excipients. Existing information can also identify which excipients need risk assessment. It should be noted that existing information is imperfect. For example, while it is possible to ask manufacturers for more information regarding excipients contained within their product, there is no legal obligation for them to share known quantitative excipient information with health professionals or make this information freely available to the public for medicines put on the market before 2010. Since 2010 new medicines authorised in Europe have to stipulate the quantitative details of important excipients in the Summary of Product Characteristics (SPC) [10].

New medicines containing potentially hazardous excipients are being developed or reformulated. At the clinical coalface, decisions continually have to be made regarding how to choose between medicines and pick the most suitable product available based on the end-users needs. Many medicines, especially when used to treat neonates, do not exist in a suitable dosage form to allow administration to a neonate so 'adult' dosage forms have to be manipulated and compounded into an age-appropriate product. This typically means addition of excipients to the original product in order to protect or stabilise the new formulation and make it palatable. There is a tendency to apply the precautionary principle as justification for excluding excipients from medicines given to neonates. The precautionary principle involves a clear balance of risks and benefits [11]. Medicines containing excipients have benefits, and the benefits will not be possible in the absence of excipients in many cases. This means that excluding excipients will not always be appropriate. The absence of evidence about harm for some excipients is likely to indicate that the excipient is not associated with harm, rather than being a cause for concern. On the other hand, many excipients can be avoided with changes in manufacturing processes without altering the pharmaceutical quality of the medicine. People who develop and use neonatal medicines need a framework to follow to help them make these important choices. When excipients are necessary it is important to have a clear rationale for this so that drug development is expedited and clinicians know what they are working with.

As a starting point we note that IPEC has proposed an approach to the safety evaluation of excipients [12]. This has the following steps:

Phase 1 *In vitro* assays to determine the potential genotoxicity, cytotoxicity, and metabolism and the ability of the compound to be absorbed across biological membranes. At the outset it is recommended that a quantitative structure–activity relationship (QSAR) model is developed. If appropriate these are followed by in vitro genotoxicity and cytotoxicity assays.

Phase 2 If the data developed in phase 1 reveals limited or no concern for toxicity, then the compound is tested in repeat-dose toxicity studies with the intention that these additional tests will be compliant with FDA guidance for excipient testing.

Phase 3 In this final stage of excipient development, many of the studies outlined in FDA's excipient testing guidance would be conducted (e.g. safety pharmacology). Based on the outcome of testing in phase two, definitive developmental and reproductive toxicity studies may be warranted. For developmental studies, a second species would be necessary.

The IPEC proposal for the safety evaluation of excipients conspicuously does not mention children, or the implications for risk management of differences in absorption, distribution, metabolism and elimination (ADME) seen in other special populations (seniors, pregnant women). With regard to children, the role of excipients is important in the development of new medicines. Regulators in Europe and the USA expect new medicines to be available in age-appropriate formulations. One feature of an age-appropriate formulation is that any excipients in the formulation do not pose unacceptable risks to the recipients of the medicine [13].

Table 1
Excipients that are potentially harmful in neonates, their application and safety concerns (adapted from [3]).

Excipient	Functional category	Applications	Reported hazards, not necessarily in neonates
Known to cause harm as an excipient to neonates			
Propylparaben	Antimicrobial	Antimicrobial activity against yeasts and molds	Hyperbilirubinemia in neonates. Irritant in injections/ophthalmic drugs. Hypersensitivity reactions [20,21]. Oestrogenic effects. Effects on cell biology.
Saccharin sodium	Sweetening	0.02–0.5% w/w	Urticaria with pruritus and photosensitivity reactions [22]
Benzyl alcohol	Antimicrobial, solvent	Up to 2% v/v in parenteral/oral preparations, typically 1% v/v.5% v/v and up used as solubilisers. 10% v/v local anaesthetic properties (parenterals, ophthalmic solutions, ointments)	Headache, vertigo, nausea, vomiting, diarrhoea, metabolic acidosis, seizures, gasping. Hypersensitivity; fatal toxic syndrome in premature infants. Pain on injection [20,21,23] Risk of hyperbilirubinaemia in neonates [24]
Benzalkonium chloride	Antimicrobial, antiseptic, solubilising, wetting	Ophthalmic preparations—preservative, 0.01–0.02% w/v;In combination with other preservatives	Ototoxic when applied to ear, skin irritation and hypersensitivity Bronchoconstriction in asthmatics. Eye irritation. Irritation to nasal mucosa [20,21,23,25]
Propylene glycol	Antimicrobial, humectant, plasticiser, solvent, stabilizing, water-miscible co-solvent	Humectant—topical—approx.15%. Preservative—solutions/semisolids—15–30%. Solvent or cosolvent: aerosol solutions 10–30%, oral solutions 10–25%, parenterals 10–60%, topical 5–80%	Skin irritation, laxative effects, contact dermatitis. [4] High doses—cardiovascular, hepatic, respiratory adverse events [23] Acute renal failure/metabolism [26]
Polysorbate 80	Dispersing, emulsifying, non-ionic surfactant, solubilising, suspending, wetting	Emulsifying: alone in oil-in-water emulsions 1–15%; in combination 1–10%. To increase water-holding prop of ointments 1–10%. Solubilising: poorly soluble APIs in lipophilic bases 1–5%; insoluble APIs in lipophilic bases 0.1–3%	E-Ferol syndrome—thrombocytopenia, renal dysfunction, hepatomegaly, cholestasis, ascites, hypotension, metabolic acidosis [21]. Inhibition of p-glycoprotein with potential effects on the blood–brain barrier and drug–drug interactions [27].
Ethanol	Solvent		CNS depression—muscle incoordination, visual impairment [21]. Negative synergic effects on CNS when associated with propylene glycol [23]. Chronic toxicity [24].
Known to cause harm as an excipient to older age groups			
Sodium metabisulphite	Antimicrobial, antioxidant	Antioxidant in oral, parenteral, and topical formulations: 0.01–1.0% w/v, i/m. Antimicrobial: syrups.	Hypersensitivity, paradoxical bronchospasm, wheezing, dyspnoe and chest tightness in asthmatic children [20,21,23]
Colloidal anhydrous Silica	Adsorbent; anticaking; emulsion stabiliser; glidant; suspending; tablet disintegrant; thermal stabiliser; viscosity-increasing	Improves flow properties of dry powders (0.1–0.5%) (tableting); stabilises emulsions (1.0–5.0%); thixotropic thickening/suspending (2.0–10.0%); in aerosols to promote particulate suspension, eliminate hard settling, minimise clogging of spray nozzles (0.5–2.0%)	A possible sarcoidosis-inducing antigen [28]
Anhydrous sodium hydrogen phosphate (monobasic, dibasic)	Buffering; emulsifying; sequestering.	Buffering agent; sequestering agent. Concentrations are dependent on the formulation.	Gastrointestinal (GI) disturbances including diarrhoea, nausea, and vomiting [21]
Sodium bicarbonate	Alkalizing; therapeutic.	To produce or maintain an alkaline pH in a preparation	Exacerbation of chronic heart failure in elderly [21]
Macrogols—polyethylene glycol	Ointment base; plasticiser; solvent; suppository base; tablet and capsule lubricant.	High molecular weight macrogols can be used as lubricants in tablet (formulations); water solubility and bad penetration through skin makes them useful as ointment bases	Hypersensitivity reactions, hyperosmolarity, metabolic acidosis, and renal failure in burn patients [21]
Trometamol	Buffering	Buffering agent, buffer range from 7.1 to 9	Hypersensitivity reactions [29]
Cetostearyl alcohol	Emollient; emulsifying; viscosity-increasing.	Increasing viscosity; stabilises emulsions; co-emulsifier; decreasing the amount of surfactant required	Hypersensitivity reactions [21] Contact dermatitis [30]
Sodium lauryl sulphate	Anionic surfactant; detergent; emulsifying; skin penetrant; tablet and capsule lubricant, wetting		Irritation to the skin, eyes, mucous membranes, upper respiratory tract, and stomach [21]
Sorbitan stearate	Dispersing; emulsifying; nonionic surfactant; solubilising; suspending; wetting	When used alone produces water-in-oil emulsions/microemulsions. In combination with polysorbate produces water-in-oil or oil-in-water emulsions/creams.	Hypersensitive reactions [21]
Likely to cause harm to neonates			
Lactic acid	Acidulant	In injections in the form of lactate as a source of bicarbonate (0.012–1.16%)	Neonates have difficulty in metabolizing R-lactic acid, and this isomer and the racemate should therefore not be used in infants aged less than 3 months old [21]
Likely to cause harm as an excipient			
Sodium cyclamate	Sweetening	0.17% w/v as sweeter, in combination with saccharin	Photosensitivity [21]
Disodium edetate	Chelating	Forms stable water-soluble complexes with alkaline earth and heavy-metal ions; concentrations 0.005–0.1%	Local inflammatory reactions [21]
Gelatin	Coating; film-forming; gelling; suspending; tablet binder; viscosity-increasing	Tablet binder; microencapsulation	Local irritation. Hypersensitivity reactions, including serious anaphylactoid reactions [21]
Triethanolamine	Alkalizing; emulsifying		Hypersensitivity, skin irritant [21]

(continued on next page)

Table 1 (*continued*)

Excipient	Functional category	Applications	Reported hazards, not necessarily in neonates
		When mixed in equimolar proportions with a fatty acid an emulsifying agent to produce fine-grained, stable oil-in-water emulsions will be formed (2–4%)	
Cresol	Antimicrobial preservative; disinfectant.	Antimicrobial preservative in parenterals (0.15–0.3%)	Skin hypersensitivity reactions [21]
Maltose	Sweetening; tablet diluent	Osmotic–ophthalmic drops and parenteral inf.	Single report of hyponatremia in a liver transplantation patient [21]
Likely to cause harm as a substance			
Sorbic acid	Antimicrobial	As antimicrobial preservative (0.05–0.2%)	Irritant and allergic hypersensitivity skin reactions [20,21]
Boric acid	Antimicrobial, buffering	As antimicrobial preservative in eye drops. Good buffering capacity to control pH.	Poisoning—abdominal pain, vomiting, diarrhoea, erythematous rash, CNS depression. Convulsions, hyperpyrexia, and renal tubular damage [21]
Borax	Alkalizing; antimicrobial; buffering; disinfectant; emulsifying; stabilizing	Antimicrobial preservative in eye preparations	Vomiting, diarrhoea, erythema, CNS depression, and kidney damage [21]
Glycine	Buffering; bulking; freeze-drying; tablet disintegrant; wetting	Cofreeze-dried excipient in injectable formulations	Disturbances of fluid and electrolyte balance; cardiovascular and pulmonary disorders [21]
Calcium chloride dihydrate	Antimicrobial, water-absorbing	Dehydrating properties	Stomach and heart disturbances. Eye irritant, dermatitis [21]
Leucine	Antiadherent; flavouring; lubricant	As antiadherent to improve the deagglomeration	Toxicities have been reported following subcutaneous administration [21].
Titanium dioxide	Coating as opacifier, pigment	As a white pigment and opacifier	Possibly carcinogenic [31]
Benzethonium chloride	Surfactant, antiseptic, wetting and/or solubilising	As an antimicrobial preservative (0.01–0.02% w/v)	Probably neurotoxic [32]
Erythrosine	Cherry-pink/red synthetic coal tar dye	Dye	Toxic to human lymphocytes in vitro, binds directly to DNA [33]
Ethylendiamine	Counter ion	Counter ion of theophylline	Hypersensitivity reactions [34,35]
Macrogol cetostearyl ether	Emulsifying; penetration enhancer; solubilising; wetting	Solubilising agent, enhancing effect on skin permeation	Toxicity has been reported [21]
Copovidone	Film-forming; granulation aid; tablet binder	As a film-forming agent (0.5–5%); tablet binder (direct compression and wet granulation) (2.0–5.0%)	Toxicity has been reported following ingestion including gastric disturbances [21]
Sodium formaldehyde sulphoxylate	Antioxidant	Antioxidant in parenteral, rectal solutions	Toxicity has been reported following ingestion [21]
Castor oil	Emollient; oleaginous vehicle; solvent.	extended release agent	Contact dermatitis [21]
Acacia	Emulsifying; stabilizing; suspending; tablet binder; viscosity-increasing.	Viscosity increasing agent (as it is in powder for oral suspension)	Hypersensitivity reactions [21]

It is clear that some medicines administered to neonates will contain excipients that should trigger a safety assessment. The IPEC proposal is not readily applicable to risk assessment of excipients in neonates, particularly with existing excipients. We propose a complementary approach adapted to neonates. Regulators will need to mandate safety testing for selected excipients in neonates. There will be a need to select excipients for safety studies and to evaluate the data arising from the safety studies. This could involve "weight of evidence" similar to approaches used in chemical safety assessment [14]. Evaluation is also relevant "downstream" that is when giving existing, or extemporaneously compounded, medicines to neonates.

Explicit risk management of excipients has not been part of the approach to neonatal medicines. In order to promote science-based evaluation we borrow frameworks for risk assessment and risk management from food safety as a model.

We will examine methodological issues relating to:

1 How to scope the size of the problem
2 How to find relevant information
3 How to weigh up the relevant information

We will also offer a preliminary framework for making choices about neonatal excipients and reflect on future directions, including the use of the food safety model.

2. Background

2.1. The clinical context

Excipients need careful consideration in neonatal practice for two reasons. Firstly, neonates are uniquely vulnerable to adverse reactions from Active Pharmaceutical Ingredients (APIs) or excipients. These vulnerabilities arise from age-specific effects on the ADME of APIs and excipients [15,16].

Secondly, neonates display specific pathologies. Neonates are babies within 28 days of their expected date of delivery. All neonates have age-specific immune dysfunction which makes them vulnerable to a range of infections. In preterm neonates age-specific pathologies include surfactant deficient lung disease, bronchopulmonary dysplasia, necrotizing enterocolitis, retinopathy of prematurity, intraventricular haemorrhage

Fig. 1. Risk analysis framework. The FAO–WHO promote risk-based approaches for the management of public health hazards in food. The approach used is called risk analysis, and is made up of three components: Risk assessment; Risk management; Risk communication.

Table 2
Definitions of steps in risk management adapted for the analysis of risks of excipients in neonates.

Term	FAO–WHO Definition	Proposed definition for neonatal excipient risk analysis
Risk assessment	The scientific evaluation of known or potential adverse health effects resulting from human exposure to foodborne hazards. The definition includes quantitative risk assessment, which emphasises reliance on numerical expressions of risk, and also qualitative expressions of risk, as well as an indication of the attendant uncertainties.	A situation-appropriate evaluation of clinically relevant effects of excipients
Hazard identification	The identification of known or potential health effects associated with a particular agent.	The identification of known or potential health effects associated with a particular agent.
Hazard characterisation	The qualitative and/or quantitative evaluation of the nature of the adverse effects associated with biological, chemical, and physical agents which may be present in food. For chemical agents, a dose–response assessment should be performed. For biological or physical agents, a dose–response assessment should be performed if the data is obtainable.	The qualitative and/or quantitative evaluation of the nature of the adverse effects associated with excipients. A dose-concentration assessment should be referenced if the data is obtainable.
Exposure assessment	The qualitative and/or quantitative evaluation of the degree of intake likely to occur.	The qualitative and/or quantitative evaluation of the degree of exposure likely to occur.
Risk characterisation	Integration of hazard identification, hazard characterisation and exposure assessment into an estimation of the adverse effects likely to occur in a given population, including attendant uncertainties.	Situation-appropriate integration of hazard identification, hazard characterisation and exposure assessment into an estimation of the adverse effects likely to occur in a given population, including attendant uncertainties.
Risk management	The process of weighing policy alternatives to accept, minimise or reduce assessed risks and to select and implement appropriate options	The process of weighing policy alternatives to accept, minimise or reduce assessed risks and to select and implement appropriate options
Preliminary risk management activities	The establishment of a risk profile to facilitate consideration of the issue within a particular context, and provides as much information as possible to guide further action. As a result of this process, the risk manager may commission a risk assessment as an independent scientific process to inform decision-making.	The establishment of a risk profile to facilitate consideration of the issue within a particular context, and provides as much information as possible to guide further action. As a result of this process, the risk manager may seek further information at a later date.
Evaluation of risk management options	The weighing of available options for managing a food safety issue in light of scientific information on risks and other factors, and may include reaching a decision on an appropriate level of consumer protection. Optimisation of food control measures in terms of their efficiency, effectiveness, technological feasibility and practicality at selected points throughout the food-chain is an important goal. A cost–benefit analysis could be performed at this stage.	Is the weighing of available options for developing or administering medicines that contain an excipient. May include reaching a decision on an appropriate level of monitoring. A cost–benefit analysis could be performed at this stage.
Implementation of the risk management decision	Will usually involve regulatory food safety measures, which may include the use of HACCP. Flexibility in the choice of individual measures applied by industry is a desirable element, as long as the overall programme can be objectively shown to achieve the stated goals. Ongoing verification of the application of food safety measures is essential.	Tailored to clinical situation
Monitoring and review	Is the gathering and analyzing of data so as to give an overview of food safety and consumer health. Monitoring of contaminants in food and foodborne disease surveillance should identify new food safety problems as they emerge. Where there is evidence that required public health goals are not being achieved, redesign of food safety measures will be needed.	Is the gathering and analyzing of data so as to give an overview of excipients individually and overall.
Risk communication	Is an interactive process of exchange of information and opinion on risk among risk assessors, risk managers, and other interested parties.	

Adapted from:

http://www.who.int/foodsafety/micro/riskassessment/en/index.html
http://www.who.int/foodsafety/micro/riskmanagement/en/index.html
http://www.who.int/foodsafety/micro/riskcommunication/en/index.html
All last accessed 6th February 2013.

and periventricular leucomalacia. Term neonates may present with hypoxic ischaemic encephalopathy, persistent pulmonary hypertension of the newborn or meconium aspiration. Each of these conditions requires specific treatments which may not be relevant to older age groups.

A wide range of excipients has been related to potential harm in neonates. A limited number of these harms have been fatal or disabling. These include polysorbate-80 [9] and benzyl alcohol [17]. Many thousands of neonates have been exposed to these excipients without suffering any obvious harm. Other examples are given in Table 1 which is reprinted from Lass et al. [3] reporting excipients contained in medicines that were administered to neonates in Estonia. This table illustrates the broad range of excipients that neonates are exposed to, many of them without obvious adverse events. It also shows the broad range of potential hazards that may be encountered. Some of these hazards are unlikely to manifest in neonates. For example hypersensitivity reactions to any substance are extremely rare in neonates. Others are theoretical possibilities. Chemicals with the potential to cause adverse effects may also be present in medical devices [18,19]. We would advocate a similar approach to devices.

The European Medicines Agency (EMA) has recently published a draft Guideline on pharmaceutical development of medicines for paediatric use which includes a section on excipients [13]. This includes a useful approach to risk assessment and a flow chart that illustrates the hierarchy of extant guidance about excipients in children. That guideline does not indicate how to handle uncertainty or to balance potential risks in regulatory issues or clinical practice. At present, the state of the art is to acknowledge concerns and uncertainty but not to propose a way forward. Examples of this are published elsewhere [3,5,6,22,36–38]. Here we propose a way forward based on the systematic evaluation of hazards, exposure and risks using methodologies that have been developed in other fields.

This approach has been influenced by the needs of people working on the clinical coalface, Nurses, Physicians and Pharmacists who have

to make real-world decisions. However, stakeholders who are more remote from the prescription and administration of medicines need to know about the constraints that clinical decision-makers operate under.

Clinical decisions include: whether to prescribe a medicine if the API can only be given with a potentially harmful excipient; whether to purchase a cheaper product that contains excipients or a more expensive product that does not contain excipient; whether to import a product licensed in another jurisdiction that does not contain excipients or to undertake extemporaneous compounding or manipulations with material that is available more conveniently.

These decisions need to be made in the absence of detailed information about the associations between exposure to excipients and outcomes. Pharmaceutical scientists and manufacturers can facilitate these decisions by providing detailed information about excipients and by taking account of the clinical reality when designing and testing formulations. Measurement of neonatal exposure to excipients will clarify some issues. We have developed the relevant methodologies and these are described below.

2.2. Need for a systematic approach to neonatal excipients

Pharmaceutical quality assurance involves ensuring that the product meets the requirements of patients or their surrogates [39]. This means that there is a need to build awareness of medicines use into all aspects of the medicine lifecycle. This awareness needs to include risk assessment of excipients. The development of a risk assessment for excipients draws on multiple sources of information. For neonates these include data from older human populations and data from case studies. Studies in animals can provide relevant information. However, they are rarely conducted in juvenile animals. Models of reproductive or development toxicology often expose pregnant animals to excipients. This gives some useful information but does not match the biological issues faced by ex utero neonates. Studies may have been conducted for a particular market e.g. the assessment of parabens in cosmetics [40]. Reviews of this body of work may inform neonatal risk assessment in part without addressing all the important points.

Risk assessment requires rigor. In particular there is a need to identify strengths and weaknesses of data explicitly. Transparency is essential to meet the needs of all stakeholders. Given that new information will continue to arise and that risk assessment is iterative, the process of risk assessment needs to be repeatable. These features are found in the FAO/WHO risk assessment and risk management models we have selected "Principles and Methods of the Risk Assessment of Chemicals in Food" Environmental Health Criteria 240 (EHC 240) [41]. This provides a framework and a range of techniques that can be adapted to specific cases. Similar frameworks have been proposed for other problems such as environmental risk exposure [42] and chemicals [43]. Such frameworks drive clarification through explicit formulation of the problem and facilitate decisions about when to act, what to do and when it is reasonable to gather more information before making decisions. We have used food safety as a model because administration of food is purposive, albeit with unintended ingredients or contaminants. Excipient exposure is often purposive unlike many environmental or chemical exposures. An alternative approach would be ICH Q11 [44]. However, Q11 is about managing risk of a process before administration. We note that although some of the terms overlap between Q11 and EHC240 the meanings of some terms (such as "risk analysis") differs between the two documents.

2.3. Proposal for risk analysis of neonatal excipients

In this section we propose an adaptation of WHO definitions to excipients [41]. We need to recognise the need for pragmatic action rather than a detailed theoretical grounding. We will never have complete data so the community needs strong, shared habits for dealing with uncertainty. The overall framework is summarised in Fig. 1 and is described in more detail in Table 2.

It is conceivable that polypharmacy in sick children will lead to multiple sources of excipients. If the same excipient is present then the expected exposure will be additive. If multiple excipients are present individual exposures may be estimated. Additional concerns will only arise if there are grounds to believe that the excipients will have synergistic effects on identified targets. In that case there may need to be an assessment of the scope of synergies, similar to that outlined for chemicals in food (Section 7.3 in EHC 240, [41]). One example is the anti-retroviral agent Kaletra which was associated with adverse events in neonates within 14 days of birth. This agent contains ethanol and propylene glycol. Propylene glycol is metabolised to ethanol so that ethanol may competitively inhibit the metabolism of propylene glycol [45]. Of note, this interaction could be predicted on the basis of known biochemistry.

Allergy, hypersensitivity or anaphylactic events following excipient exposure are a theoretical possibility. Food safety includes risk assessment in food allergy (Section 4.10 of EHC 240) [41] which relates exposure to symptoms. The absence of commonly reported symptoms of allergy or hypersensitivity in neonates renders this concern difficult to assess but the lack of reports about allergy in neonates in general is reassuring.

Once the information has been gathered, it is necessary to make decisions. Different approaches are available. These include weight of evidence and the application of the precautionary principle [46,47]. Whichever is chosen it is important to remember that medicines containing excipients are beneficial and that there are important non-clinical considerations such as the marketability of medicines for relatively small neonatal population. For acutely administered medicines standard approaches to toxicity can be used. For chronic exposure health-based guidance values can be selected and justified on a case-by-case basis.

These examples point to the need to account for the whole process of manufacture and administration, particularly during regulatory approval. Medicines are administered to neonates by a variety of routes using a range of devices. This variation should be accounted for including the possibility of interactions with devise used to administer medicines (e.g. leaching) if this is relevant. In many cases it will be possible to quickly rule out likely effects from past experience of exposures in other populations. This will be coupled with limits of exposure that include a generous difference between what is known to cause harm and the amount of excipient that a baby is exposed to. So-called "conservative safety margins" or conservative "safety factors" provide a margin of error when extrapolating between data sources. Clinicians should be alert to the possibility that the medicines they use have unexpected effects due to excipients. It is important that manufacturers share the quantitative composition of their products so that others can see the justification for assumptions that excipients are safe.

3. Hazard identification and characterisation: what are the potential problems with neonatal excipients?

A hazard relates to the "inherent property of an agent or situation capable of having adverse effects on something" [41].

Hazards known from other age groups may not be relevant to neonates. This may relate to differential expression of the targets of toxicity at different ages. In principle this may also relate to age-specific differences in ADME. For example, foetal and neonatal liver is adapted to deal with transplacental xenobiotics and may be "better" at some types of metabolism than the liver in other age groups.

Hazards may be unique to neonates. There are a number of age-specific windows for development. Disruption of these windows may lead to irreversible effects on organ development. While these windows are well described during teratogenesis they are also relevant in the third trimester and first month after birth at term. The theoretical

possibility of disruption to development is not enough to prompt the avoidance of a drug or an excipient. It is necessary to assess the risk in the light of a balanced assessment of potential benefits and harms.

3.1. Finding relevant information

Systematic reviews for different substances used in neonates and their impact on this specific population are required. Here we outline points to consider when developing an efficient, reliable and sustainable approach to identifying hazards relevant to neonates (Fig. 2).

A search needs to start with a research question, for example: "What do we know about the consequences of exposure with this compound?" This can include human of all ages and relevant animal data. This then needs to be formulated for the target databases, including PubMed, Embase, Web of Science, International Pharmaceutical Abstracts, Biosis and Pascal. One useful starting point will be the Database of Safety and Toxicity of Excipients in Paediatrics (STEP) hosted by the European Paediatric Formulation Initiative [48].

There are two main challenges when searching for information about excipients that is relevant to neonates. Firstly, information about excipients is found in many sources and many study designs. The types of publication that will be encountered include clinical studies: Case Reports, Epidemiological, pharmacokinetics and non-clinical studies: toxicologic, toxicokinetic and mechanistic. There are no index terms that differentiate between studies of chemicals per se and studies of chemicals as excipients. Secondly, neonates have many descriptive terms. Also, some animal models are relevant and others are not. These two challenges make it very difficult to design specific searches.

Our initial searches for evidence about propylene glycol that is potentially relevant to neonates yielded 35,000 hits. In order to overcome the challenges we refined the search process with five logical steps.

1. Database exploration: search and analysis to identify if it provides sufficient hits to be included in the search
2. Sieving: narrow the search by removing the irrelevant references
3. Refine database search sentence
4. Performance: use the sentence in the database
5. Evaluation: compare with reference set

For example in our refined search about propylene glycol we located 1500 relevant hits from six databases.

Once the literature search has been completed, a second sieve is required.

A panel of experts is needed to focus the work on neonates and rank articles according to their usefulness and relevance.

4. Exposure assessment

Our working definition of exposure assessment is "the qualitative and/or quantitative evaluation of the degree of exposure likely to occur". The word "exposure" has different meanings in different disciplines. We distinguish between exposure to medicines assessed by examining prescription data and the exposure to excipients assessed by examining the content of medicines or the circulating concentrations of excipients. For existing excipients exposure assessment methods available from food safety and pharmacoepidemiological studies can be applied but the process may not be straightforward [49,50]. Considering distinct population specific features like intake pattern (e.g. specific disease spectrum or rapid growth rate related food intakes) or data sources as well as available resources (human as well as funds) are of paramount importance [51]. Direct measurements of circulating concentrations are required when the administered dose has a reasonable chance of generating circulating concentrations that approach a conservative safety margin. The choice of excipients reflects previous safe use in adults. One view is that excipients that have not caused problems in older age groups can be assumed to be safe in neonates, unless there is biological evidence to the contrary. An alternative view is that there are significant differences between age groups with respect to pharmacokinetics and pharmacodynamics of many drugs. Similar differences may be found for some excipients. As noted elsewhere, the existence of this possibility should not, in itself, be used to remove excipients from products used in neonates.

4.1. Exposure to medicines—describing the use of medicines using pharmacoepidemiological methodologies

4.1.1. Methods and opportunities

Different study designs can be applied in pharmacoepidemiology, all with their own specific indications, advantages and disadvantages [50]. Retro- or prospective cross-sectional cohort studies and health care database analyses have been most commonly used. The details of these

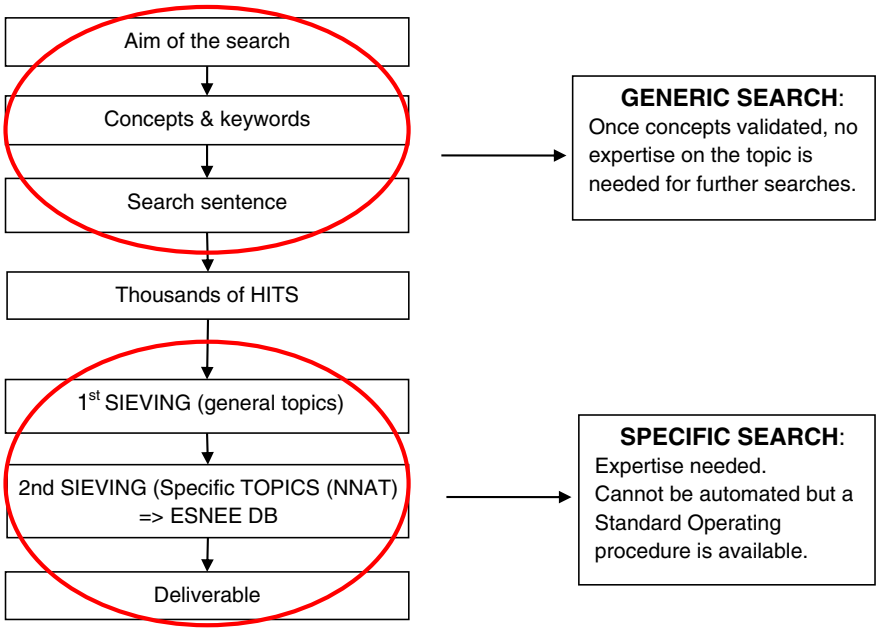

Fig. 2. Search strategy for information relating to safety of excipients in neonates.

Table 3
Advantages and disadvantages of different study designs in excipient exposure assessment using pharmacoepidemiological methods.

Study design	Advantages	Disadvantages
Case control	–Allows to compare a limited number (1–3) of excipients of interest –Allows rich data-collection	–Data collection is limited to 1 or 2 centres –Previous experience in research is needed –Resource consuming
Retrospective cohort studies	–Allows data collection over prolonged time periods –Feasible without previous research experience –Allows rich data-collection	–Data quality questionable and cannot be fixed –Resource and time consuming
Prospective cohort design	–Allows data collection over prolonged time periods –Allows real time data correction –Allows individualised approach and multiple data collection	–May not be feasible in multicenter/multinational setting –Resource and time consuming
Point prevalence study	–Allows multinational studies –Allows individualised approach –Allows multiple data collection –Time and resource saving	–Covers very short time-periods –Under- or overestimates exposure of rarely used medicines –Prone to significant bias is very small datasets
Service evaluation survey	–Allows multinational studies –Allows data collection over prolonged time period –Time and resource saving –No need for special training	–No individualised data –Limited amount of data –Under- or overestimates exposure of rarely used agents
Health care database analyses	–Allows multinational studies –Allows long-term collection of multiple data –Time and resource consuming (even if databases available) –Allows individualised approach	–Most databases register prescription not consumption rates –Variability of available exposure data potentially results in biased risk estimates

different approaches have been discussed elsewhere [50,52]. Advantages and disadvantages of different study designs in excipients studies are summarised in Table 3.

4.1.2. Selecting the most appropriate methods to estimate neonatal exposure to excipients

One aim of studying the use of medicines that contain excipients is to define market sizes that will justify reformulation or product substitution. Accordingly it is important to use research methods that can be applied in large multi-country populations. The feasibility of linking multi-country databases to study country specific drug use in a systematic manner without being hampered by methodological differences has been proven [53]. However, data sources applied in such studies may not contain information crucial for excipient studies, like formulation, trade name and manufacturer details. While these data may be available on sales level, individual exposures are of relevance. Furthermore, the uncertainty rising from the variability of available exposure data potentially results in biased risk estimates [54]. Addressing neonatal population with the vast majority of drug/excipient exposures in acute care/in-hospital setting further limits available data sources.

Point prevalence studies (PPS) in which the prescribing information is collected within a pre-specified time-point, have been widely used in describing antibiotic consumption [55–60]. PPS is easy to perform, especially when targeting large populations, does not require significant amounts of highly qualified personnel, allows collecting individualised data (e.g. age, gender, dosing regimen, indication) and captures prescribing variability of drug and excipient use. However, due to extremely short reporting period (usually one day) less frequently used medicines may be either under- or over reported (Table 3). PPS may be inappropriate in small cohorts (e.g. single centre studies). Repeated cross-sectional interviews have been found a valid proxy for chronic drug exposure but are not appropriate for drugs used irregularly [61].

Unit level observations are useful midpoint between sales data and PPS. An example of a unit level observation is a service evaluation survey (SES) in which units are asked which medicines they administer to neonates over a specified period. SES allow long term cohort recruitment and have proven an effective tool in rare disease surveillance in multicenter settings [62]. In reporting drug exposure outcomes adding a longitudinal dimension has proven of value, as trends can be more accurately studied and projections of future trends improved [63]. However, depending on the outcomes studied, effect of the participants' previous experience should be anticipated. With large volumes of data reported (like in excipient studies) and especially prolonged recall periods decreasing compliance and underestimation may occur [64]. Furthermore, not only optimal recruitment of participants but also sample size maintenance over the course of a study becomes of vital importance [63].

The most accurate information could be collected from long term cohort studies as described by Lass et al. [65]. This approach, however, is extremely time and resource consuming and may not be feasible in multinational settings. However, this design may be valuable in studies evaluating only a limited number of agents/excipients.

4.1.3. Calculating required sample size

In order to achieve generalisability of the results sample size calculation is of paramount importance in observational studies. In studies on neonatal intensive units (NICUs) the recruitment of participating centres, regional distribution and variability in levels of care and unit size as well as response rate need to be considered. As random recruitment is often unfeasible, cluster approach may be used. Recruitment of randomly chosen regional clusters based for example on the EuroStat NUTS classification would allow adjusting for the variability of levels of care in NICU studies. Still in cluster design the cluster effect and intracluster coefficient of variance need to be considered. Participation of all available centres in a region/cluster may also be difficult to achieve.

For example, for a Europe-wide NICU study assuming a neonatal admission rate of 15% [66–69] and a response rate of 50–70% [70–73]; based on the EuroStat NUTS (or equivalent if NUTS classification not available) regional distribution of the population and reported nationwide birth rates, the number of potentially available neonatal admissions can be calculated and the representative sample size estimated for each country and region [74]. Inflating the estimated sample size by cluster design effect, based on the variance of cluster size and applying a fixed intracluster coefficient of variance of 0.001, suggested for mean cluster size exceeding 100 [75] for a $\pm 5\%$ accuracy of the estimate the required sample size will be 10,000 participants recruited from more than 100 NICUs of all European countries.

4.1.4. Existing data on neonatal exposure to excipients

Only a few studies have looked at the excipients exposure in children. In a UK based study [6] Whittaker et al. described that during the hospital stay 38 premature neonates infants were exposed to over 20 excipients including ethanol and propylene glycol, chemicals of known neurotoxicity. They also looked at the extent of exposure in

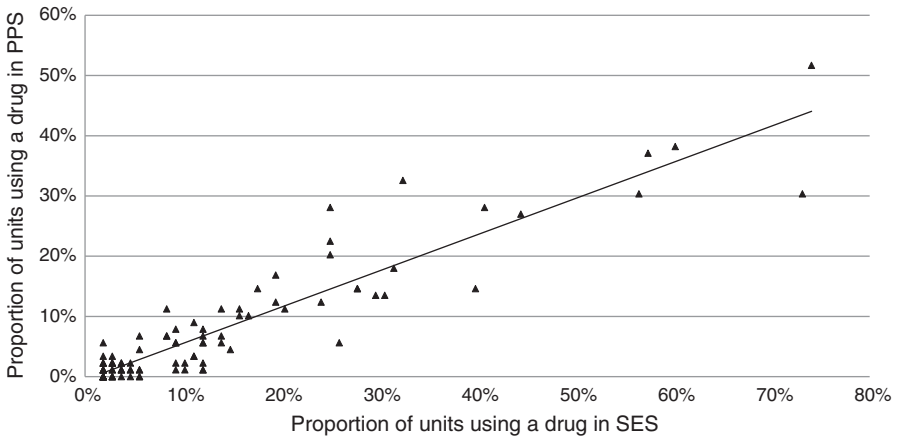

Fig. 3. Correlation in proportion of units using a medicine between service evaluation survey and point prevalence study ($R^2 = 0.9605$).

terms of quantitative amount of ethanol, sorbitol and propylene glycol. By calculating age-corrected exposure of the above mentioned excipients the authors showed that in several neonates weekly exposure exceeded that considered safe in adults. In another prospective cohort study in Estonia by recording all medicines (n = 93) used in hospitalised neonates (n = 490) over six months we describe the use of 123 different excipients. Eight known to be toxic excipients were given within 51% of neonatal medicines [3].

The European Study for Neonatal Excipient Exposure (ESNEE) provides a useful case study for exposure studies. Considering the above and the primary aim of the ESNEE project of defining tools for excipient risk assessment (and not excipient exposure outcome reporting) a two-step cross- sectional approach was chosen. First a three-day SES created a comprehensive list of drugs and excipients prescribed to neonates in European NICUs and described their frequency of use at the unit level. The SES served as a basis for the PPS in unit selection, testing of power calculation hypothesis as well as creation of a prepopulated web-based database to improve reporting quality. The PPS aimed to assess individual excipient exposure of neonates to provide basis for excipient kinetic studies; highlight needs and opportunities for product substitution and priorities for reformulation; describe variations of prescribed drugs and excipients exposure rates between European countries and in different demographic groups among neonates. The feasibility of the two-step approach is well characterised by the correlation of the unit level quantitative results obtained in the two studies (Fig. 3).

Thus either of these approaches can be used, depending on the resources available and the purpose of the study.

4.2. Exposure to excipients: describing the content of medicines

A major challenge in describing excipient use is finding data on excipient content of pharmaceutical products that were awarded a marketing authorisation before 2010. For identification of excipients in each unique medication the Summaries of Product Characteristics (SmPC) is the best available source. However, until now only qualitative and not the quantitative information on excipients can be found from SmPCs. If the SmPC is not available or the drug is not registered searches of the homepages of manufacturers or credible public databases (e.g. www.diagnosia.com) can be performed or the SmPC can be requested direct from the manufacturers via their medicines information departments. The complexity of the search process is well characterised by the fact that data on qualitative excipient composition in ESNEE project were unattainable for 13% of the 1065 reported drugs (data in file of ESNEE project). In addition, one should bear in mind that after reviewing national SmPCs unification of synonyms according to the European pharmacopeia and integration of excipients with identical chemical base into one is still required.

4.2.1. Importance of sharing data on excipients

Knowledge of the qualitative and quantitative composition in terms of the active substance(s) and any excipients included within a formulation is essential for correct administration of a medicinal product [76]. Thus, this type of information should be freely accessible to all (healthcare professionals and members of the public) so that prescribers are able to make fully informed decisions and evaluate which product is the most appropriate for the end user needs.

One of the main issues is product variation. Even the same manufacturer can produce two different strengths of an Active Pharmaceutical Ingredient (API) which have different amounts of a specified excipient(s) or contain completely different excipients altogether. Patients tend to assume generics are identical and do not realise different manufacturers are able to include different excipients with the same API. This lack of standardisation can leave patients at risk unless the user is clearly aware of what excipients are actually contained within the product that is being administered to them.

Especially within the "Specials" market, many licensed manufacturing units can offer an alternate excipient-free version of a product, at a cost. But how do we know what is available on the market if this data is not freely accessible to all health professionals? And should companies be forced to only include excipients if their presence is vital to the formulation? We would distinguish between manufacturing and usability. It may be possible to manufacture a formulation without excipients but longterm stability and microbiological stability could be harmed.

In the UK, quantitative information has been made available to the ESNEE investigators by companies and by the National Competent Authority (Medicines and Healthcare Regulatory Authority, MHRA) under strict conditions. Quantitative information was requested for specific excipients of interest and not all elements of a complete formulation. The data will be presented unlinked to specific products. The combination of company and regulatory sources yielded data for the majority of products of interest in the UK. This approach shows that quantitative information about excipients can be made available for specific purposes.

4.3. Exposure to excipients: describing the circulating concentrations of excipients in neonates

Epidemiological knowledge about the extent of excipient administration enhances our understanding of exposure. More specific information of the exposure of individual neonates is essential to relate what is known about excipients to the effects on babies. The administered dose may not be absorbed. Neonates have relatively higher water content and relatively lower fat content than other age-groups which will have

implications for the volume of distribution of excipients. The ontogeny of hepatic xenobiotic metabolism has significant effects on the circulating concentrations of many chemicals. Elimination is different in neonates; renal clearance is significantly less in this age group than in older people [16].

In the past, studies of excipient kinetics have not been possible because of limits on sample volume and difficulties applying classical pharmacokinetic methods to the samples that can be taken from neonates. A baby may have a circulating volume of 80–90 mL/kg. The total circulating volume in the smallest babies (500 g) may only be 40 mL while the largest newborns will have a circulating volume of 450 mL. This is coupled with immature haematopoiesis and repeated blood sampling in sick babies. The amount of blood that can be sampled is limited: the European Medicines Agency recommends that sampling is limited to 1% of circulating volume any one time and a total of 3% of circulating volume from all research activity over a 28 day period [77]. In practice, sample volumes need to be less than 100 μL. These limitations limit the applicability of traditional "rich" sampling approaches.

These problems have now been overcome. Excipients can be measured in microsamples of less than 50 μL. Neonatal pharmacokinetic studies often use sparse sampling because study samples are most conveniently taken at the same time as routine clinical samples. Population pharmacokinetic models can be built using sparse samples. The ESNEE group has developed microsample assays for ethanol using a static headspace gas chromatography coupled mass spectrometry (GC–MS) method [78] for methyl paraben and propyl paraben using liquid chromatography–tandem mass spectrometry [79] [S. Yakkundi, personal communication] and for benzoic acid [S. Yakkundi, personal communication]. Similar work has been done for propylene glycol using high performance liquid chromatography with photodiode array detection [80,81]. These methodologies can be extended to the majority of known excipients, or excipients under development. Microdosing studies using ^{14}C-labelled agents are feasible in this age-group and could also be used in excipient kinetic studies (M. Turner, personal communication).

This means that it is now possible to examine the net effects of age-specific features of excipient disposition. The assessment of potential excipient exposure can include direct evidence about the concentrations that results from prescribed medicines administered during clinical care. The inclusion of this information in risk assessment will reduce uncertainty and inform the development of safety margins.

For some excipients, the literature may help define relevant excipient-dynamic markers. Future studies that determine excipient exposure as well as excipient-dynamic markers may allow the quantification of the excipient concentration–toxic effect relationship which could contribute to assessments of tolerable intake. Excipients that originate from the environment may complicate the interpretation of kinetic studies.

5. Risk characterisation

Our definition of risk characterisation is: "Situation-appropriate integration of hazard identification, hazard characterisation and exposure assessment into an estimation of the adverse effects likely to occur in a given population, including attendant uncertainties." Approaches to risk characterisation have been summarised [82,83]. Here we focus on identifying neonatal outcomes of interest and, relating outcomes to exposure.

5.1. Description of outcomes

The neonatal literature includes short-term and long-term outcomes of exposure to excipients. These reports are predominantly opportunistic, most often arising from adverse events. This means that these reports are filtered through several biases including ascertainment bias and reporting bias. This means that the literature may not give a complete picture of the outcomes associated with excipients exposure in neonates. Short-term outcomes may have a significant impact, although often the importance of a short-term impact is unclear. It may be difficult to assess whether long-term outcomes are attributable to an excipient. The API may be prescribed to sick babies leading to confounding by indication since an adverse outcome may be due to the disease state rather than the excipient.

5.2. Relating outcomes to exposure

A range of approaches are available to relate outcomes to exposure [82,83]. In order to illustrate the possibilities in neonates we provide some case studies.

5.2.1. Parabens

Acute hazards seen in neonates associated with parabens include hyperbilirubinaemia. There are also concerns about the possibility of oestrogenic effects and cell physiology. Each of these effects could cause adverse long-term outcomes. Excipient kinetic studies in human neonates would allow estimate of whether paraben concentrations come close to concentrations known to have oestrogenic effects. In order to move from assessments of exposure based on estimates of intake, the ESNEE project is conducting studies to define the kinetics of methyl paraben and propyl paraben in neonates.

The risk assessment of parabens needs to account for their beneficial effects as antimicrobials. The withdrawal of parabens from multi-use preparations may increase the incidence of infection in neonates who have age-specific vulnerabilities to a number of microorganisms. The EMA has published a reflection paper on parabens. This concludes that "the use of methylparaben in oral formulations up to 0.2% of the product is not a concern for humans including the paediatric population whatever the age group". To date there are insufficient PK data to make recommendations for propylparaben in neonates although from the age of two years onwards a permitted daily exposure of 5 mg/kg/day would be safe. Alternative preservatives are available but there are significant costs to developing new formulations.

5.2.2. Propylene glycol

Hazards associated with propylene glycol relate to the buildup of propylene glycol when it is administered in concentrations greater than the metabolic capacity of the patient. The manifestations of this include biochemical (increased anion gap and osmolar gap) and clinical (metabolic acidosis, seizures and coma). These have been documented in all human age groups when high doses of propylene glycol are administered [84–88,8,89–91]. In older age groups these references suggest that doses up to 1 g/kg/day are unlikely to cause acute adverse effects. It appears that toxicity is apparent with plasma concentrations greater than 1 mg/mL. The pharmacokinetics of propylene glycol has been described in adults [92], children [84,92] and neonates [93]. In principle a physiologically-based toxicokinetic approach can be applied to the methods for threshold-based toxicity [82]. The key issue will be the concentration at which toxic effects are found in neonates: a ten-fold safety margin may not account for the variability in ADME seen in neonates. The threshold for toxicity may be altered by co-exposure to ethanol, as exemplified by issues with Kaletra [45]. However, surveillance in routine clinical practice has shown that currently available medicines that contain propylene glycol are not associated with an increased incidence of adverse events [94].

Long term effects of propylene glycol are more difficult to identify. The US National Toxicology Program Center for the Evaluation of Risks to Human Reproduction Monograph on propylene glycol states that propylene glycol is "probably not" associated with adverse effects on human development [26]. One approach is to assess which biological processes are relevant to long-term outcomes. The toxicology of these effects can be studied in other species or in vitro and then bridged to humans. For example exposure to propylene glycol is associated with

apoptosis in the brain of 4 days old mice. Four day old mice were exposed to intraperitoneal doses of [95].

No toxic effects were seen at intraperitoneal doses of propylene glycol of 1 mL/kg or lower. The authors estimate that a neonatal dose of 40 mg/kg Phenobarbital (containing 68% propylene glycol) would deliver a dose of 0.2 mL/kg. If mouse and neonatal human phenobarbital PK are similar, then routine clinical exposures appear to have at least a 5-fold safety margin for the adverse effects seen in mice. The comparisons are rendered less precise by the absence of mouse PK data.

Conventionally, a safety factor of a 10-fold difference is used to account for variation between species and a further 10-fold difference is applied to account for variation within humans [82,83]. Given that the mouse intraperitoneal/brain model suggests a 5 fold safety margin there may be grounds for concern that preparations of Phenobarbital contain amounts of propylene glycol that are relevant to the clinical situation.

5.2.3. Sodium metabisulphite

Acute hazards associated with sodium metabisulphite include hypersensitivity and bronchial spasm/wheeze. These have not been reported in neonates, perhaps because immune processes to support hypersensitivity are not functional at this age and because airway muscle works differently. Harms that may be associated with long-term adverse outcomes include neurotoxicity in mice. When sodium metabisulphite was applied to cortical neurons from day 14.5 embryo mice or astroglial cells cultured from mice aged 0–2 days there was a dose-dependent increase in neuronal cell death. The effects became apparent at concentrations 10 times higher than those which would be expected in the circulation of preterm neonates [96]. Circulating concentrations may not reflect brain concentrations. Nevertheless these observations are relevant to neonates. Sodium metabisulphite is found in medications administered before and after preterm birth. One example is a corticosteroid given to women at risk of preterm birth, dexamethasone. The administration of corticosteroids to women at risk of preterm birth is associated with reduced mortality in those babies that are subsequently born prematurely. Observational studies showed that administration of perinatal dexamethasone was associated with worse outcomes than perinatal hydrocortisone [97]. Since there are preparations of dexamethasone (and other steroids) that do not contain sodium metabisulphite these results were sufficient to prompt product substitution. While there is data to support a dose–response relationship in animals direct bridging to neonates has proved difficult because of problems developing an assay for sodium metabisulphite that can be used in human toxicokinetic studies.

Sodium metabisulphite is also found in inotropes which are commonly used in to treat haemodynamic insufficiency during the days following birth [98]. The relevant APIs, dopamine and dobutamine are susceptible to oxidation so that an antioxidant is used to maintain the stability of the drugs, most commonly sodium metabisulphite [99]. The APIs alone, and in combination with sodium metabisulphite are neurotoxic in vitro [100]. If it is not possible to formulate these APIs without an antioxidant then the net effect of the medicine should be assessed, for example by including excipient-free placebos in Phase 3 randomised controlled trials.

5.2.4. Polysorbate 80

Polysorbate 80 is implicated in acute hazards that appear to be specific to neonates. This association stems from an epidemic of an unusual clinical syndrome described in 1984 shortly after a new preparation of Vitamin E was introduced—a preparation that contained high concentrations of polysorbate 20 and polysorbate 80 [9]. The syndrome included thrombocytopenia, renal dysfunction, hepatomegaly, cholestasis, ascites, hypotension, metabolic acidosis. Reports of the epidemic described the syndrome including dose response relationships for each element of the formulation. The syndrome only occurred in neonates who received more than 20 U/kg/day of E-Ferol. Adverse effects were associated with a dose of Polysorbate 80 greater than 72 mg/kg/day and a dose of Polysorbate 20 at least 8 mg/kg/day [9].

In this case the lowest observable adverse effect dose can be estimated from clinical data, for severe adverse effects at least. This could be used as a "critical effect" for estimates of exposure limits for severe adverse effects. There is little data that is relevant to less severe effects or to long-term effects. There is also no data about the relationship between intake of polysorbate 80 and circulating concentration in neonates. In principle it is possible to conduct such studies using the concentrations that would be used in novel formulations.

6. Risk management

Risk managers will be clinicians as well as manufacturers and regulators. This means that risk assessors need to communicate with people who are not specialists in risk assessment or toxicology.

6.1. A model for decision-making

The most important step is to avoid excipients if possible. Many APIs are available in formulations that do and do not contain excipients. In these cases, the excipient-free product will be preferable, all things being equal. In some settings the cost of excipient-free products is excessive or there are other practical reasons why an excipient must be used. If excipients are not avoidable due to formulation or practical issues a rigorous approach would consider: the risk arising from the illness being treated; the extent to which that risk will be ameliorated by a particular medicine; the risk from the excipients; the impact of the hazard attributable to the excipients. This approach would consider the best case scenario of an effective medicine and the worst case scenario of an ineffective API and harmful excipient. In many cases this will be a thought experiment, given the lack of data. Clinical judgment is needed but clinical judgments are best done with a structure and documentation. Excipients may be acceptable after a rigorous risk assessment.

6.2. Approaches to risk management during medicines development

Our suggestions about how to manage risk are:

Use a structured risk assessment to triage which excipients are likely to be harmful: some excipients have been widely used without any obvious adverse effects and can continue to be used at doses known to be safe and tolerable. It is possible that neonates will be exposed to excipients from sources other than medicines. This possibility should be included in the risk assessment rather than be used as a reason to avoid excipients in medicines.

New medicines with existing excipients

- The benefits of medicines will depend on the total (net) effects of the combination of API and excipient, as will the risks. In order to define the net effects of the combination it is necessary to ensure that placebos do not contain excipients of concern.
- In early phase (uncontrolled) studies of medicines that require excipients accept the risk of the integrated medicine because it is important to define the dose or efficacy of the medicine. These studies will have enhanced safety assessments so that hazards arising from the excipient will be detected.
- Include monitoring for significant excipient hazards in risk-based post-marketing surveillance if the risk assessment procedure indicates that this is appropriate.

New excipients

- Consider a broad range of potential neonatal indications for medicines that contain the novel excipients when defining the novel pathway.

- Add selected age-appropriate tests of the excipient to the proposed development pathway (including pre-clinical work) in the light a structure risk assessment procedure that account for the potential neonatal indications.

7. Conclusion

Many excipients have been used without adverse events in the newborn period and excipients will continue to be required in this age group. Rational medicines use will depend on structured risk assessment. We have outlined the issues relating to the risk assessment of excipients in neonates. We have described the difficulties inherent to hazard identification and exposure assessment. These difficulties need to be accounted when safety assessment of existing excipients are planned. They are also relevant to the assessment of novel excipients. We advocate a structured approach to identifying relevant information and acknowledging uncertainties. We envisage that this will allow regulators, manufacturers and clinicians to avoid or use excipients appropriately. This would optimise care by minimizing harm from potentially toxic excipients and avoid opportunity costs arising from the inappropriate avoidance of excipients.

Conflicts of interest

- M.A. Turner is Chair of the European Network for Paediatric Research at the European Medicines Agency (EnprEMA)
- J.C. Duncan—None
- U. Shah—None
- T. Metsvaht—None
- H. Varendi—None
- G. Nellis—None
- I. Lutsar—is a member of the EMA Paediatric Committee
- S. Yakkundi—None
- J.C. McElnay—None
- H. Pandya—None
- H. Mulla—None
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- A. Rieutord—None
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