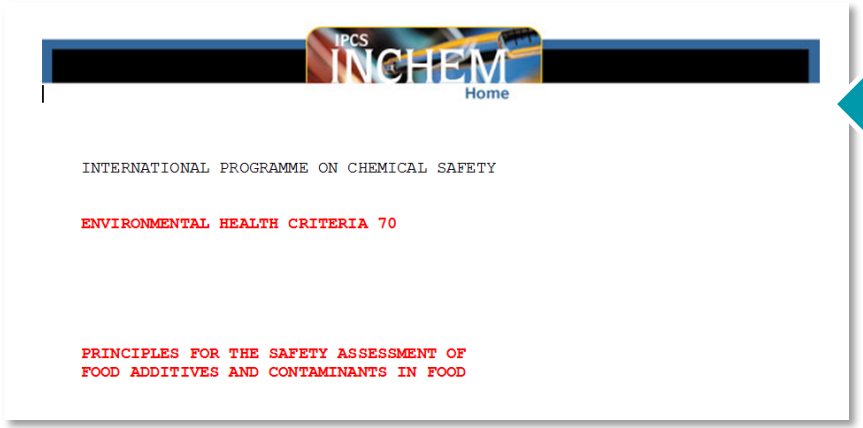
Guiding principles on the risk assessment of substances present in foods intended for infants below 16 weeks of age

Ursula Gundert-Remy
Chair of the FAF WG on re-evaluation of food additives permitted in foods for infants below 16 weeks of age

efsa
European Food Safety Authority

IPCS 1987

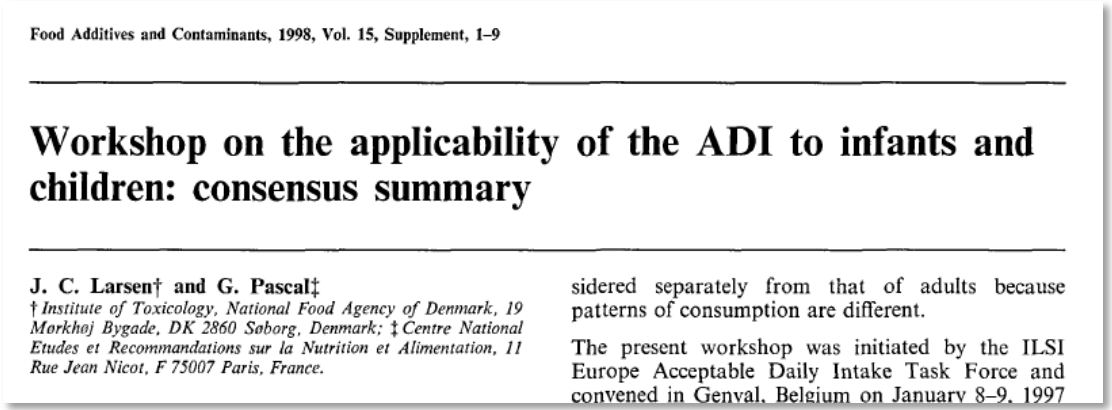


Infants particularly sensitive to the harmful effects of foreign chemicals

Immaturity of protection mechanisms (metabolism and elimination, gut and blood-brain barrier)

General vulnerability of rapidly growing tissues

1997 ILSI WORKSHOP



Food Additives and Contaminants, 1998, Vol. 15, Supplement, 1–9

Workshop on the applicability of the ADI to infants and children: consensus summary

J. C. Larsen† and G. Pascal‡
† Institute of Toxicology, National Food Agency of Denmark, 19 Mørkhøj Bygade, DK 2860 Søborg, Denmark; ‡ Centre National Etudes et Recommandations sur la Nutrition et Alimentation, 11 Rue Jean Nicot, F 75007 Paris, France.

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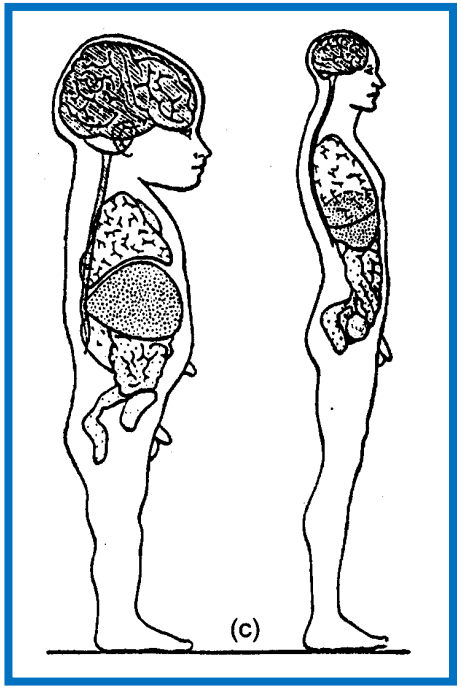
THE DEVELOPING INFANT – THE FIRST FOUR MONTHS

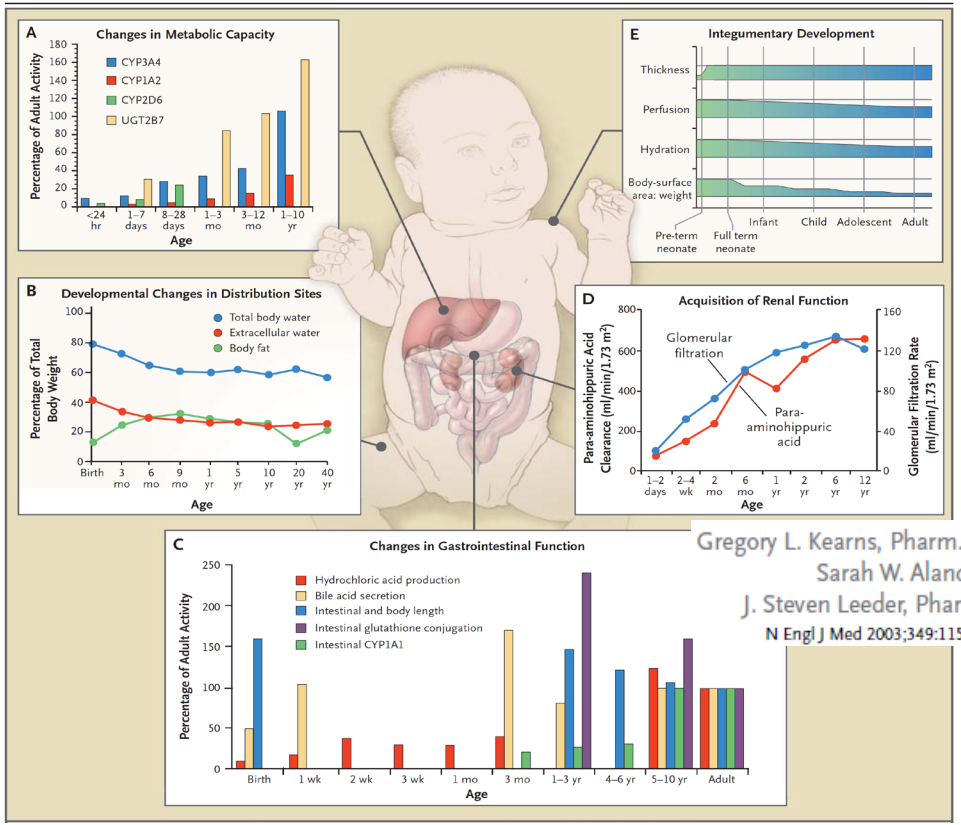
Newborn babies are not scaled down adults!



PHYSIOLOGICAL SPECIFICITIES – RELEVANT FOR TOXICOKINETICS

Metabolism

Distribution



Excretion

Gregory L. Kearns, Pharm.D., Ph.D., Susan M. Abdel-Rahman, Pharm. Sarah W. Alander, M.D., Douglas L. Blowey, M.D., J. Steven Leeder, Pharm.D., Ph.D., and Ralph E. Kauffman, M.D.

N Engl J Med 2003;349:1157-67.

A FEW WORDS ABOUT THE DEVELOPING INFANT….

Absorption of substances might be slower but amount absorbed not changed

Distribution:

neonates: larger extracellular and total-body water spaces and lower fat content

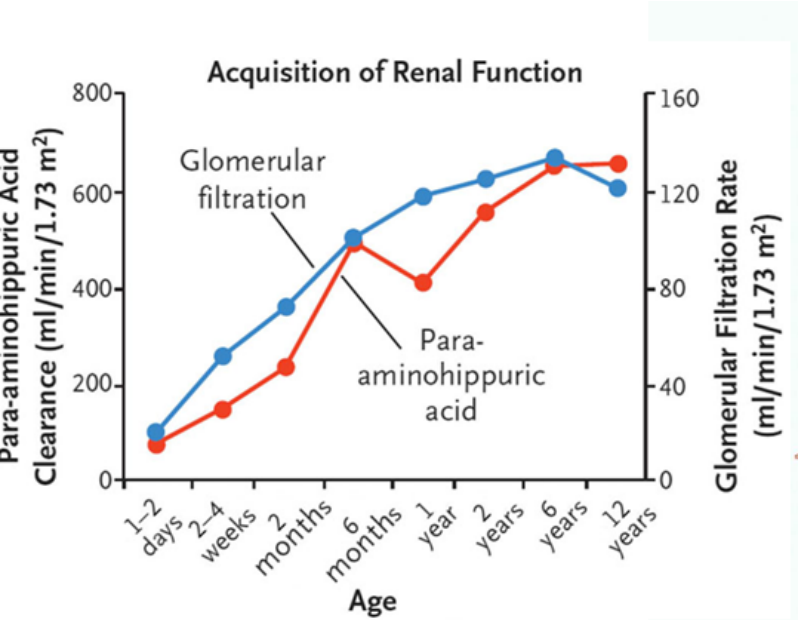
Changes in regional blood flow and reduced total plasma proteins (esp. albumin)

Metabolism and excretion:

Unique pattern of development for Phases I & II metabolism but well characterised

Overlapping substrate specificities and reduced regional blood flow: overall impact on clearance is limited

DEVELOPMENT OF EXCRETORY FUNCTIONS



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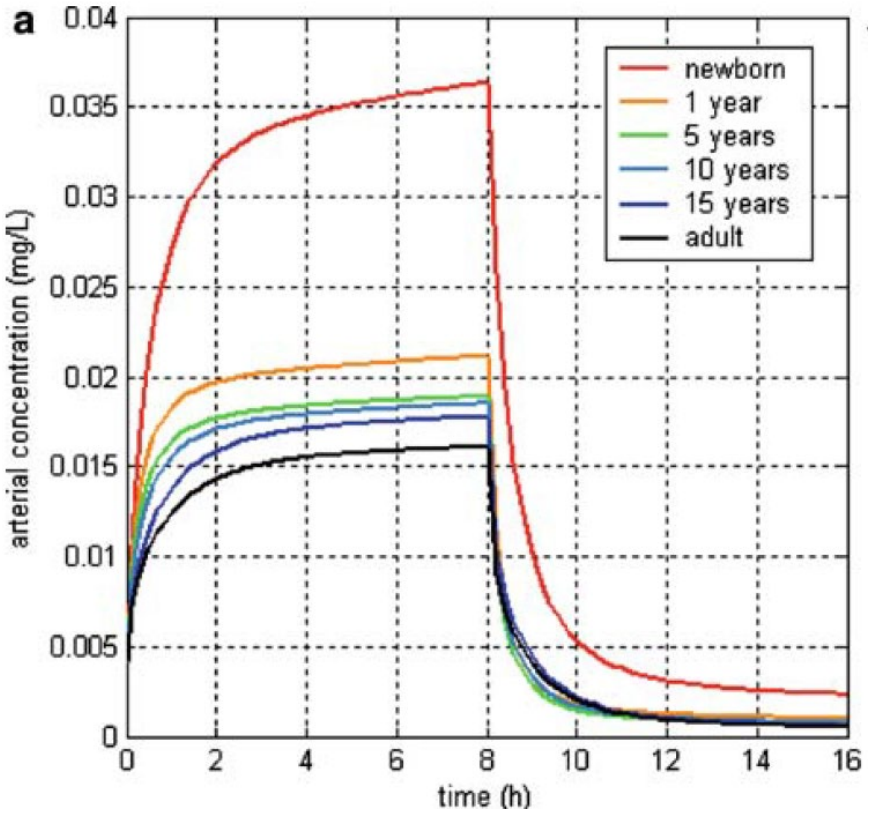
See also

Cresteil, T. (1998). Onset of xenobiotic metabolism in children: toxicological implications. *Food Additives & Contaminants*, *15*(S1), 45-51

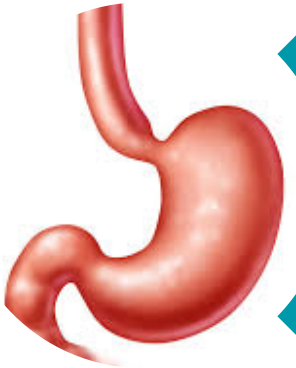
CONTINOUS ADMINISTRATION AND RESULTING BLOOD LEVEL IN DIFFERENT AGES



The resulting blood level is 2.3 fold higher in the newborn compared to the adult

Abraham K, Mielke H, Huisinga W, Gundert-Remy U Arch Tox , 2005

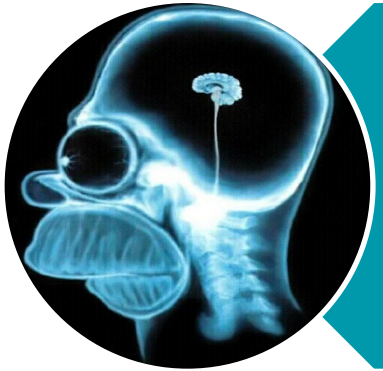
FURTHER ASPECTS IN THE DEVELOPING INFANT



Now considered approaching maturity at birth

Higher intragastric pH (higher than 4)

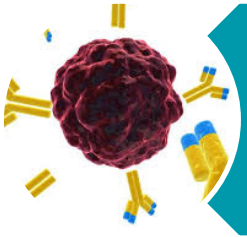
Reduced gastric propulsion



Blood brain barrier now considered approaching maturity at birth

Differences in permeation may render the infant brain more susceptible but this is currently not predictable.

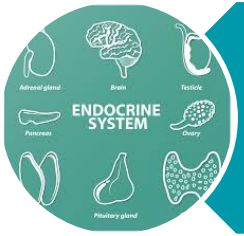
TOXICOLOGICAL TARGET ORGANS IN THE DEVELOPING INFANT



Vulnerable and susceptible to conditions influencing the developing immune system

Reproductive organs are immature at birth

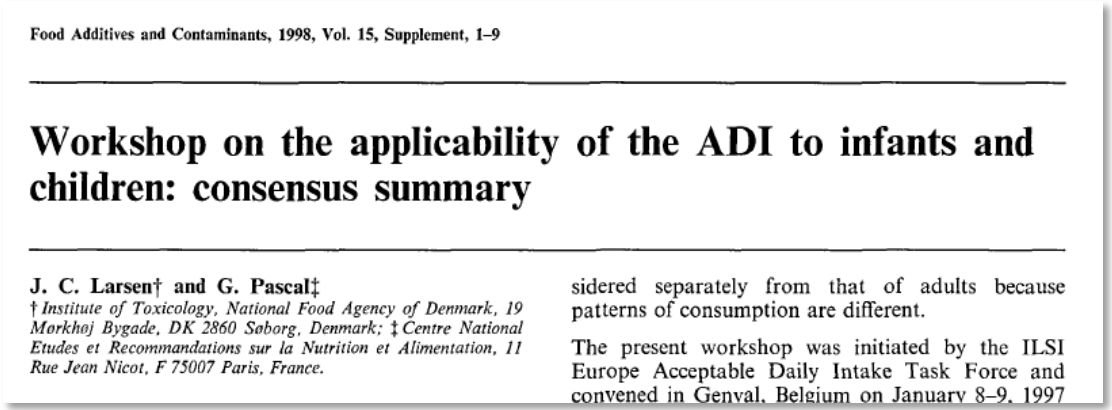
Male system sensible (Sertoli cells)



Unique endocrine profiles different from those in the adult

Effects specifically thyroid at early developmental stage may be reflected in deficits at later time points

1997 ILSI WORKSHOP



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EFSA Journal

SCIENTIFIC OPINION

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Guidance on the risk assessment of substances present in food intended for infants below 16 weeks of age

EFSA Scientific Committee,
Anthony Hardy, Diane Benford, Thorhallur Halldorsson, Michael John Jeger,
Helle Katrine Knutsen, Simon More, Hanspeter Naegeli, Hubert Noteborn, Colin Ockleford,
Antonia Ricci, Guido Rychen, Josef R Schlatter, Vittorio Silano, Roland Solecki,
Dominique Turck, Jean-Louis Bresson, Birgit Dusemund, Ursula Gundert-Remy,
Mathilde Kersting, Claude Lambré, André Penninks, Angelika Tritscher,
Ine Waalkens-Berendsen, Ruud Woutersen, Davide Arcella, Daniele Court Marques,
Jean-Lou Dorne, George EN Kass and Alicja Mortensen

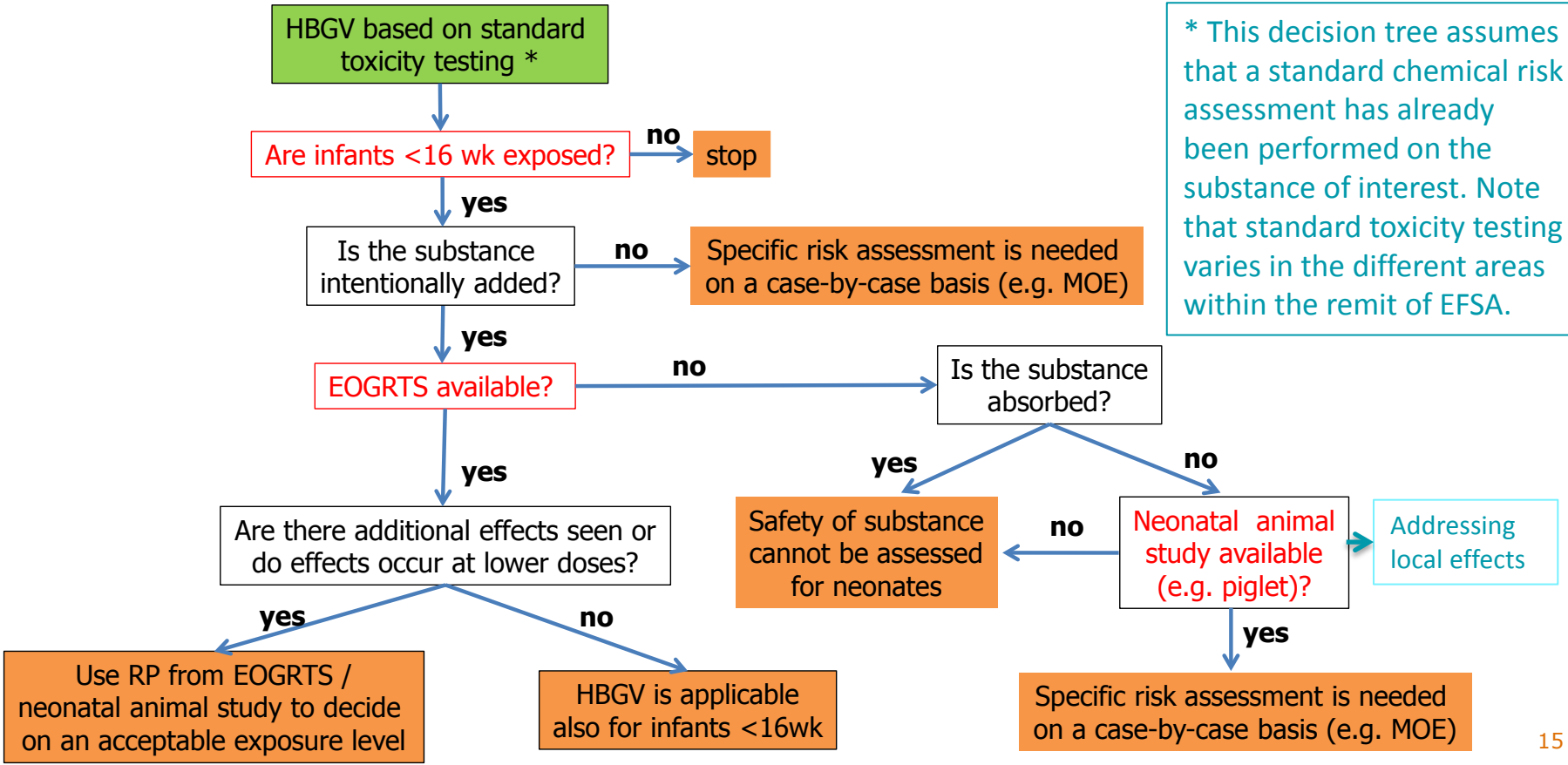
ELEMENTS TAKEN INTO CONSIDERATION IN THE GUIDANCE

- For the exposure assessment: formula as the only source of nutrition in non-breastfed infants
- Impact on toxicokinetics:
  - the absorption of the substance from the GI tract
  - reduced renal excretion
  - metabolism in the neonatal organism compared with the adult
  - compensation by an additional factor of 3 for substances not intentionally added when no information on TK behaviour in adult and neonatal organism exists
- Knowledge of organ development (critical windows) in infants
- The overall toxicological profile of the substance from the standard toxicological tests (critical effects)

EXTENDED ONE GENERATION REPRODUCTIVE TOXICITY STUDIES

- EOGRTS informs on effects of exposure of neonatal animals at equivalent life stages of human infants
  - Allows for direct dosing of the neonatal animals
- Helps to identify, by comparison with standard toxicological studies, whether
  - additional relevant effects occur or
  - the effects occur at lower doses in the neonatal animals

DECISION TREE FOR THE RISK ASSESSMENT: Food for infants



* This decision tree assumes that a standard chemical risk assessment has already been performed on the substance of interest. Note that standard toxicity testing varies in the different areas within the remit of EFSA.

Thank you for your attention