# SPANZA Advisory on neurotoxicity of general anaesthesia for infants and children

Society for Paediatric Anaesthesia in New Zealand and Australia

## Development Group

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## Needs statement:

Neurotoxicity associated with general anaesthesia in infants and children is an area of controversy in the practice of clinical anaesthesia. Clinicians who provide anaesthetic care for paediatric patients require a summary of the available evidence to guide decision making and to inform advice given to parents and families.

## Aims:

1. To summarise the evidence on neurotoxicity from general anaesthesia in children.
2. To provide practical advice for anaesthetists and proceduralists who treat paediatric patients in Australia and New Zealand regarding the planning of procedures requiring general anaesthesia in children.
3. To provide information that can be used to advise parents when the issue of neurotoxicity is discussed.

## Statement

### Background

In recent years there has been concern about the possible harmful effects of anaesthetic drugs on the developing brain. This concern stems from research in animals showing that anaesthetic drugs cause neuronal injury that is associated with alterations in behaviour, learning and memory. The evidence for an effect in humans is unclear. Some cohort studies have found anaesthetic exposure is associated with subsequent neurodevelopmental outcomes. However, it is often difficult to determine whether this association is due to the anaesthetic itself, the underlying medical condition or behavioural factors leading to the need for anaesthesia, the surgery, pain and inflammation that accompanies surgery, or indeed a variety of other factors. To date, the one randomised trial has shown evidence for no effect of anaesthetic drugs on neurodevelopmental outcomes.

In December 2016 the FDA released a statement advising that "…the repeated or lengthy use of general anaesthetic and sedation drugs during surgeries and procedures in children younger than 3 years or in pregnant women during their third trimester may affect the development of children's brains". SPANZA has released this statement to present a summary of the evidence and provide guidance for those who provide anaesthetic care to infants and children.

### Key points and recommendations

- Choosing appropriate outcomes for studies on neurotoxicity is difficult. Research thus far has shown no significant association between anaesthesia exposure and broad measures of intelligence; however, alterations in behaviour may better characterise the domain most closely associated with anaesthetic exposure. Research is ongoing in this area.
- In Australian and New Zealand children only undergo general anaesthesia when there is a clear clinical need.
- There are currently no alternatives to the medications used for general anaesthesia, and no other drugs or techniques have been shown to be safer than current best practice.
- If a procedure requiring general anaesthesia can be delayed, it is unclear at what age the administration of general anaesthesia would be considered less of a risk.

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## What to tell parents

- A routine discussion regarding potential neurotoxicity is not currently recommended.
- If parents request information, then based on current evidence we can say:
    - Brief (<1 hour) procedures do not appear to increase the risk of adverse outcomes in most neurodevelopmental domains including cognitive outcomes.
    - There are fewer data available to assess the impact of longer procedures (up to 4 hours). Current studies will provide more information on this in the coming years.
    - Repeated procedures requiring general anaesthesia are associated with worse neurocognitive outcomes compared to single exposures, however this may be explained by the underlying indication for the procedures rather than the anaesthesia itself.
    - There are currently no alternatives to the medications and techniques that are currently used.
    - If a procedure requiring general anaesthesia can be postponed, the benefit of earlier intervention should be weighed up against the potential for small reductions in neurocognitive outcomes.
    - The anaesthetist will ensure a child having an anaesthetic is safe and has minimal disruption to their normal physiological parameters.

## Summary

Laboratory studies have demonstrated that neonatal exposure to typical anaesthetic drugs cause specific histological changes, electrophysiological alterations and long-term behavioural changes in a variety of animal species.

Some observational cohort studies in humans have demonstrated an association between anaesthetic exposure and poor neurodevelopmental outcomes, but the magnitude of the effect is small. One clinical trial has shown no effect.

A meta-analysis of results from large studies (GAS, PANDA and MASK) found no difference in intelligence between general anaesthetic exposed and unexposed children but did find a small difference in behavioural scores.[1] This finding is in keeping with non-human primate studies and retrospective observational human cohort studies.

Our best evidence to date has shown that general anaesthesia in children has no effect on:

- Academic achievement
- General intelligence
- Memory
- Language

There appears to be an association with:

- Behavioural issues
- Executive function
- Social communication
- Motor function
- Attention Deficit and Hyperactivity Disorder

However, whilst an association can be demonstrated, the magnitude of the effect is small.[2]

Biologically it is known that anaesthetic drugs cause apoptosis, however research to date has not yet defined a specific and consistent clinical outcome that directly mirrors the histological and long-term behavioural effects of anaesthesia exposure in laboratory experiments. Whilst there has been significant progress in our understanding of the neurotoxicity of general anaesthesia, there are still many unknowns. Most studies have examined broad populations of children, however it is not known if certain sub-groups are more vulnerable. There may be genetic or epigenetic factors that are yet to be determined. In addition, surgery in children sometimes improves neurological outcomes, for example improved hearing after tympanostomy or improved psychological well-being after correction of otapostasis. The developmental benefits of surgery need to be balanced against any potential neurotoxicity risk. Finally, the critical window of exposure risk is still unclear. The FDA warning from 2016 had a cut-off of three years, however studies since then have identified risk associations at all ages less than five.[2]

Based on the current evidence there is no need to delay or avoid short procedures in children. For longer cases, there is no evidence that an alternative technique is better and if a decision is made to delay an elective case, we do not know how long to wait for there to be no risk.

It is easy to cause undue anxiety around consent for parents due to the complexity and uncertainty of the information available. It is not mandatory to provide routine information about neurotoxicity to parents, however if asked a rational discussion of the issue should occur, including a summary and interpretation of the current literature.

# Appendix A

**Summary of available evidence (October 2022)**

## Animal Studies

*Rats*

The interest in whether anaesthetic drugs can cause damage to the developing brain began after it was discovered that GABA agonists and NMDA antagonists cause accelerated apoptosis in the developing brain of a rat. Apoptosis is the process of programmed cell death and is a normal part of central nervous system development, however certain mechanisms can accelerate apoptotic neurodegeneration, including exposure to anaesthetic drugs.[3] Widespread apoptosis was seen in 7-day-old rats after exposure to a NMDA receptor antagonist.[3] The vast majority of anaesthetic drugs act on GABA or NMDA receptors and subsequent rat studies found that exposure to a variety of anaesthetic drugs including ketamine, propofol, sevoflurane, isoflurane, desflurane, benzodiazepines and nitrous oxide all resulted in accelerated neuronal apoptosis.[4,5] The effect seemed to be worse with prolonged exposure and exposure to multiple agents in combination.[6-8] Some studies have shown exposure to anaesthetic drugs causes learning and memory problems in the rat. For example, 4 hours of 1 MAC of sevoflurane has been shown to affect the memory of the exposed rat. However, if the rat was housed in an enriched environment then this effect could no longer be detected.[9] This indicates that neurodevelopment is not simple and that many factors are involved. It may also indicate that neuroplasticity is important when recovering from an insult and this may be even more relevant in humans.

*Non-human primates*

The brain development of rats is quite different to humans, therefore studies involving non-human primates offer a model that may be more appropriate to explore the potential neurotoxic effects of anaesthesia in humans. Rhesus monkeys exposed to ketamine on day 5 to 6 of life performed worse than a control group on a range of tasks related to learning and memory when tested at seven months of age.[10] Other studies have shown effects on motor and socioemotional behaviour after multiple exposures to isoflurane in Rhesus Macaques.[11] No differences were seen after a single exposure, however the infant Macaques exposed three times to five hours of isoflurane subsequently performed worse on motor tests conducted at one year of age and had increased social anxiety. Repeated exposure to sevoflurane in the first six weeks of life has also been shown to result in persistent anxiety in Rhesus monkeys when tested at 1 and 2 years of age.[12] Memory is also affected when Rhesus monkeys are exposed repeatedly to sevoflurane during infancy.[13]

*Summary of animal studies*

Animal studies have shown that exposure to anaesthetic drugs during vulnerable periods of brain development results in a detectable neurotoxic lesion. This period of vulnerability varies between species. In rodents it appears to be between postnatal days 4 and 10, which corresponds to the peak of synaptogenesis. In Rhesus monkeys high rates of synaptogenesis continue to 35 days of age. In humans, there are high levels of synaptogenesis during the third trimester and during the first 4 years of life.[14] However, different regions of the brain develop at different times and may be more susceptible to insults at certain time points. It is not clear how laboratory conclusions can be translated to human outcomes. Another major difference in most animal studies is that no surgery is conducted. It is possible that the role of stimulation and injury is important when considering neurodevelopmental outcomes. Animal studies also lack consistent physiological monitoring, demonstrated by the high mortality reported in these experiments. This leads to the possibility of poor cerebral perfusion during exposure which may be responsible for neuronal damage. However, histologically this type of excitotoxic neuronal damage appears different to the apoptotic neuronal damage seen in response to anaesthetic drugs.[15]

## Human Studies – not specific to anaesthesia

It has been established that neonates who have major cardiac or non-cardiac surgery are at increased risk of poor neurodevelopmental outcomes. Wernovsky et al. in 2005 showed that neonates with complex congenital heart disease have decreased fine motor ability, problems with memory and executive functioning and attention deficits later in life.[16] Similarly, Walker et al. in 2006 published a paper demonstrating that neonates who undergo major non-cardiac surgery, such as repair of congenital diaphragmatic hernia or oesophageal atresia, also have worse outcomes later in life, including reduction in IQ and emotional and behavioural issues.[17] The role of anaesthesia in these outcomes is undetermined.

## Human Cohort Studies – related to anaesthesia

In the last decade, researchers have explored human impacts of general anaesthesia using epidemiological data, clinical cohort studies and studies on twins. One such study examined a cohort of 5357 children born between 1976 and 1982 in Minnesota. The number of children found to have a learning disorder was 593 and the hazard ratio (HR) for one exposure to anaesthesia was 1.0 (95%CI 0.79-1.27), for two exposures was 1.59 (95%CI 1.06-2.37) and for three or more exposures was 2.6 (95%CI 1.60-4.24). This study was criticised because there were many confounders and the anaesthetic techniques used were outdated.[18] The same cohort of children were used in another study to look at the incidence of Attention Deficit and Hyperactivity Disorder (ADHD) prior to the age of 19. In this study, the authors adjusted for some confounders and found a HR of 1.18 (95%CI 0.79-1.77) for a single anaesthetic exposure prior to the age of two and a HR of 1.95 (95%CI 1.03-3.71) for multiple exposures.[19]

A more recent cohort of children from 1999 to 2002 was examined in relation to developmental delay or behavioural disorder. In this study 383 children who had an inguinal hernia repair prior to the age of 3 were matched with 5050 children with no history of surgery. The HR for a developmental or behavioural disorder was 2.3 (95%CI 1.3-4.1). The authors adjusted for age, sex, low birth weight and hypoxia, however there were many other confounders, such as socioeconomic status and parental education, that were not considered.[20] A Danish study examined a birth cohort from 1986 to 1990 and looked for an association between anaesthetic exposure and academic performance. 2689 children who had inguinal hernia repair during infancy were matched with 14575 controls. Initial results found that those who had surgery performed worse academically, however after adjusting for sex, birth weight, parental age and education, there was no difference.[21]

### *Twin studies*

One method that eliminates some of the confounders in these types of studies is to examine twins discordant for exposure to general anaesthesia. One twin study looked at a birth cohort in New York between 1999-2005 that included 10450 twin siblings. 138 twin pairs were discordant for anaesthetic exposure under the age of 3 years. There were 9 cases of developmental or behavioural disorders in those who were exposed to anaesthesia and 11 cases in those who were not exposed.[22] Whilst the numbers in this study were too small to make any definitive conclusion, the results suggested that exposure to anaesthesia may not be the causative factor related to poor neurodevelopmental outcomes. Another larger twin study from the Netherlands examined 1143 monozygotic twin pairs and their educational achievements and cognitive problems at age 12. Overall, exposure to surgery resulted in worse outcomes, however there was no difference within twin pairs discordant for exposure.[23]

### *Association with Attention Deficit and Hyperactivity Disorder*

Some large observational cohorts have found a small, but statistically significant increased risk of developmental delay or ADHD from exposure to general anaesthesia, even when adjusting for known confounders. A cohort of children from Olmsted County, Minnesota between 1996 and 2000 was studied in relation to the association between anaesthesia exposure and the diagnosis of ADHD. This study found that children exposed to two or more anaesthetics before the age of 3, were approximately twice as likely to develop ADHD in adolescence. The same effect could not be demonstrated with a single exposure.[24] Another study that found an association between anaesthesia exposure under the age of 3 and later diagnosis of ADHD involved a nationwide cohort of patients in Taiwan between 1997 and 1999. It was found that multiple exposures, or exposures greater than three hours, were associated with an increased incidence of ADHD after the age of 4 (HR 1.71 and 2.43 respectively).[25] Another cohort of 38,493 children exposed to anaesthesia under the age of 5 from Texas and New York between 1999 and 2010 were matched with 192,465 controls. The HR for developmental delay was 1.26 (95%CI 1.2-1.32) and for ADHD was 1.31 (95%CI 1.25-1.37).

### *Risk related to age of exposure*

It had long been assumed that the highest risk for poor neurodevelopmental outcomes occurs with exposure at a young age, however in the US study of 38,493 children under the age of 5 years, the risk was the same in a neonate as it was in a 4-year-old.[26] Another study that challenged the notion of higher risk at a younger age was a large Swedish cohort study of 2,174,073 children between 1973 and 1993. 33,514 of the children had a single exposure to general anaesthesia prior to 4 years of age and 3640 of the children had multiple exposures. The authors compared school grades at age 16 and IQ testing at military conscription with 159,619 controls and adjusted for sex, month of birth,

parental education, gestational age, APGAR scores, household income, cohabiting parents and number of siblings. A very small reduction in school grades and IQ was seen, however the difference was only seen if the exposure to general anaesthesia occurred between 3 and 4 years of age.[27] It is worth noting in this study that whilst a statistically significant reduction in school grades and IQ could be demonstrated, the magnitude of the effect was very small. To put it into context, a single exposure to general anaesthesia resulted in a 0.41% reduction in school grades, whereas being born in December versus January of the same year resulted in a 5.34% reduction and male gender or low maternal education both resulted in a reduction of approximately 10%.

*Studies from our region*

In Australia a cohort of 211,978 children was studied and exposure to anaesthesia prior to 4 years of age examined in relation to developmental assessments and school grades (NAPLAN scores). The adjusted odds ratio for developmental delay was 1.17 (95%CI 1.07-1.29), for scoring below average in numeracy was 1.34 (95%CI 1.21-1.48) and for scoring below average in reading was 1.23 (95% CI 1.12-1.36). The risk for developmental delay and reading were not present if only one exposure to anaesthesia occurred, however the association with poor numeracy could still be demonstrated.[28]

*Ambi-directional cohort studies*

The Paediatric Anaesthesia Neurodevelopment Assessment (PANDA) study was published in 2016 and was an ambi-directional cohort study of 105 sibling pairs. Exposure to general anaesthesia prior to 3 years of age was recorded and the primary outcome was IQ between 8 and 15 years of age. A range of secondary outcomes including memory and learning, motor and processing speed, visuospatial function, executive function and language were also examined. The median duration of anaesthesia was 80 minutes. There was no difference in IQ or in any of the secondary outcomes.[29]

PANDA looked at a single exposure, however the question of whether multiple exposures were associated with poor outcomes remained. The Mayo Anesthesia Safety in Kids (MASK) study aimed to determine if multiple exposures to general anaesthesia prior to 3 years of age was associated with adverse neurodevelopmental outcomes. Children who were unexposed (n=411), singly exposed (n=380) and multiply exposed (n=206) underwent neuropsychological testing at ages 8 to 12 or 15 to 20 years. The primary outcome was IQ (Wechsler Abbreviated Scale of Intelligence) and there were a range of secondary outcomes similar to those used in PANDA. There was evidence for no difference between the groups. A single exposure resulted in a reduction in IQ score of 0.5 points (95%CI -2.8-1.9) and multiple exposures resulted in a reduction of 1.3 points (95%CI -3.8-1.2). For the secondary outcomes, children who had multiple exposures performed worse on tests of processing speed and fine motor abilities and parents of multiply exposed children reported increased problems with executive function, behaviour and reading.[30] The authors note that the results of any of the secondary outcomes should be interpreted cautiously.

*Summary of human cohort studies*

Numerous retrospective cohort studies have been able to demonstrate an association between exposure to general anaesthesia and poor neurodevelopmental outcomes. The apparent hazard of anaesthesia exposure appears to fall below that of many better-defined neurodevelopmental risks, for example socio-economic status and maternal education.

The majority of these types of studies have not shown a consistent association between general anaesthesia and measures of intelligence, academic achievement, memory and language. There appears to be a more consistent association between general anaesthesia and deficits in behaviour, executive function, social communication and the diagnosis of ADHD. However, it should be noted that the hazard ratios reported for these associations range between 1.18 and 2.3 which suggests that if there is truly an effect, the magnitude of that effect is likely to be small.

Studies in twins discordant for exposure have not been able to demonstrate an association between anaesthetic exposure and poor cognitive or developmental outcomes. Results from some cohort studies have thrown doubt on the theory that exposure at a younger age is associated with the greatest risk of neuronal damage. All of these studies have a number of problems: they are affected by confounders, and only known confounders can be adjusted for in the final model; they use different outcomes which may miss deficits in sub-domains of neurobehavioral activity; and there are many unknowns in relation to the subjects included, such as type of surgery, type of anaesthesia and the length of exposure.

## Human Clinical Trials – related to anaesthesia

The problems with retrospective cohort studies resulted in the need for well-designed prospective clinical trials to provide more robust evidence.

The only completed randomised controlled trial to examine the issue of neurodevelopmental outcomes after general anaesthesia was the GAS trial (Neurodevelopmental outcome at 2 and 5 years of age after general anaesthesia or awake-regional anaesthesia in infancy: an international, multicentre, randomised controlled trial).[31,32] This was a randomised equivalence trial that involved 722 infants from 28 hospitals in 7 countries. The infants were randomised to receive general anaesthesia or awake-regional anaesthesia for hernia repair and the primary outcome was IQ at age 2 and 5 years (Wechsler Preschool and Primary Scale of Intelligence, third edition). The median duration of anaesthesia was 54 minutes. There was evidence for equivalence between the two anaesthetic techniques at both 2 and 5 years of age. The authors concluded that: "Slightly less than 1 hour of general anaesthesia in early infancy does not alter neurodevelopmental outcome at age 5 years compared with awake regional anaesthesia…"[32]

The question of whether a longer exposure to general anaesthesia in infancy results in adverse neurodevelopmental outcomes remains and a large, international randomised controlled trial is underway to address this issue. The TREX trial will include 450 children having long surgery (>2 hours) before the age of 2 years. The infants will be randomised to standard sevoflurane anaesthesia or low-dose sevoflurane with remifentanil and dexmedetomidine. The children will be followed up at age 3 with similar outcome measures as the GAS trial.

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