Appendix 1 (as supplied by the authors)

Table 1: Summary of evidence from a few non-human primate studies showing injury to brain cells and structure and cognitive deficits following anesthetic exposure and a study on mice demonstrating neurotoxicity and the mitigating effects of environmental enhancement (a characteristic of human society)

Drug/Authors	Study	Findings
Ketamine Zou et al[1]	Rhesus monkeys (postnatal day 5/6) given ketamine 20 mk/kg i.m.+20-50 mg/kg/hr i.v. to maintain a steady anesthetic plane for 3, 9, or 24 hr (3/group), followed by a 6-hr withdrawal period; 9 controls. Brains then dissected and examined histoimmunochemically.	No significant neurotoxic effects occurred if anesthesia duration was 3 hr. Ketamine infusions for 9 or 24 hr significantly increased neuronal cell death in the frontal cortex.
Isoflurane Brambrink et al[2]	Macaques (postnatal day 6) exposed for 5 hr of isoflurane (no movement and <10% rise in heart rate/blood pressure with limb clamping) or air (5/group), followed by a 3-hr withdrawal period. Brains then dissected and examined histoimmunochemically.	Brains exposed to isoflurane displayed significant apoptosis in both the white and gray matter throughout the central nervous system.
Isoflurane Coleman et al[3]	Rhesus macaques exposed to 5 hr of isoflurane (end-tidal 0.7-1.5 vol%) 3 times (postnatal days 6, 9,12), once (postnatal day 6), or not at all (6/group), followed by behavioral tests at 1 and 12 months.	3 exposures resulted in motor reflex deficits at 1 month, more affiliative/appeasement and anxiety behaviour at 12 months. No significant effect after 1 exposure.
Ketamine Paule et al[4]	Rhesus monkeys (postnatal day 5/6) given ketamine 20 mk/kg i.m.+20-50 mg/kg/hr i.v. to maintain a steady anesthetic plane for 24 hr. At 7 months, animals began training to perform cognitive function tasks.	At 10 months, control animals outperformed ketamine-exposed animals, and likewise for the next 10 months and at 3.5 yrs.
Sevoflurane Zheng et al[5]	Pregnant mice exposed to sevoflurane (2.5% for 2 hrs on gestational day 14) and not exposed were studied. Fetal brain tissue was immediately harvested and analyzed (6/arm). Some pregnant mice carried their fetuses to term and their offspring mice brain tissues (6/arm) were compared. Some offspring mice (15/arm) were tested in the Morris water maze at 31 postnatal days.	The fetuses and offsprings of exposed mothers had evidence of inflammation and reduced postsynaptic density in their brains. Offspring mice at 31 days showed learning and memory impairment. Environmental enhancement (training with wheels, small mazes, ladders) mitigated against the learning and memory impairment in offspring mice.

References

1. Zou X, Patterson TA, Divine RL, et al. Prolonged exposure to ketamine increases neurodegeneration in the developing monkey brain. Int J Dev Neurosci 2009; 27:727–31.
2. Brambrink AM, Back SA, Riddle A, et al. Isoflurane-induced apoptosis of oligodendrocytes in the neonatal primate brain. Ann Neurol 2012; 72:525-35.
3. Coleman K, Robertson ND, Dissen GA, et al. Isoflurane anesthesia has long-term consequences on motor and behavioral development in infant rhesus macaques. Anesthesiology 2017; 126:74-84.
4. Paule MG, Li M, Allen RR, et al. Ketamne anesthesia during the first week of life can cause long-lasting cognitive deficits in rhesus monkeys. Neurotoxicol Teratol 2011; 33:220-30.
5. Zheng H, Dong Y, Xu Z, et al. Sevoflurane anesthesia in pregnant mice induces neurotoxicity in fetal and offspring mice. Anesthesiology 2013; 118:516-26.

Appendix to: Ho A M-H, Fleming ML, Mizubuti GB. Anesthetic neurotoxicity and the developing brain: Perfect storm or tempest in a teacup? *CMAJ* 2017. doi: 10.1503/cmaj.170313