

Clinical Manifestations of Gadolinium Retention: Summary of Animal Data

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Conflicts of Interest

Employee of GE Healthcare.

Clinical Manifestations of Gd Retention in Animals

In scope



- GBCA Administration
- Retained Gd
- Macroscopic changes
- Behavioural effects

Out of scope



- Gd Salts e.g. GdCl_3
 - Acute toxicity/effects
 - Microscopic changes
 - Sub-clinical effects
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Overview

- **Macroscopic Effects**
 - Skin lesions
 - **Behavioural Effects**
 - Adult animals
 - Juvenile animals
 - In utero exposure
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Macroscopic Effects – Skin Lesions in Rats

- First reported by Harpur et al. 1993¹
- Further studies conducted in post-NSF era
- Skin reddening, fur loss, scab formation and ulceration
- Seen with high (4xHED) repeated doses of Omniscan/gadodiamide in naïve and nephrectomised male rats^{2,3,4}



¹Harpur et al. Invest Radiol. 1993 Mar;28 Suppl 1:S28-43.

²Sieber et al. Eur Radiol. 2008 Oct;18(10):2164-73.

³Pietsch et al. Invest Radiol. 2009 Apr;44(4):226-33.

⁴Grant et al. Acta Radiol. 2009 Mar;50(2):156-69.

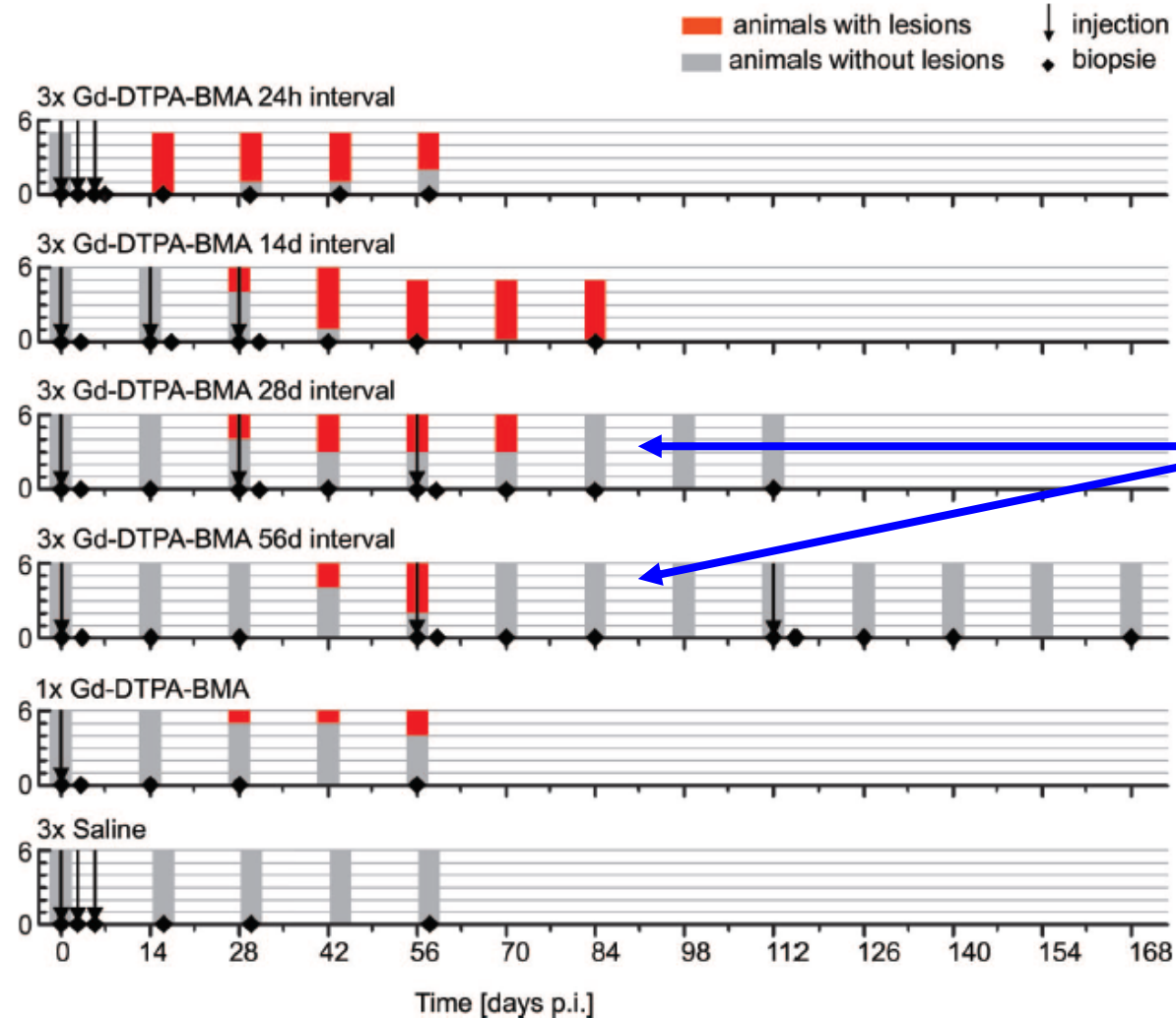
Skin Lesions not observed in Females or Primates

“At necropsy, treatment-related findings in males in the 5.0-mmol/kg group included skin desquamation (90%) and sores (60%)”¹ This effect was not seen in female animals.

**Skin lesions were not observed in male or female monkeys
28 repeated high doses, 4xHED daily, 112xHED total cumulative dose¹**

Available data indicate this effect is specific to male rats

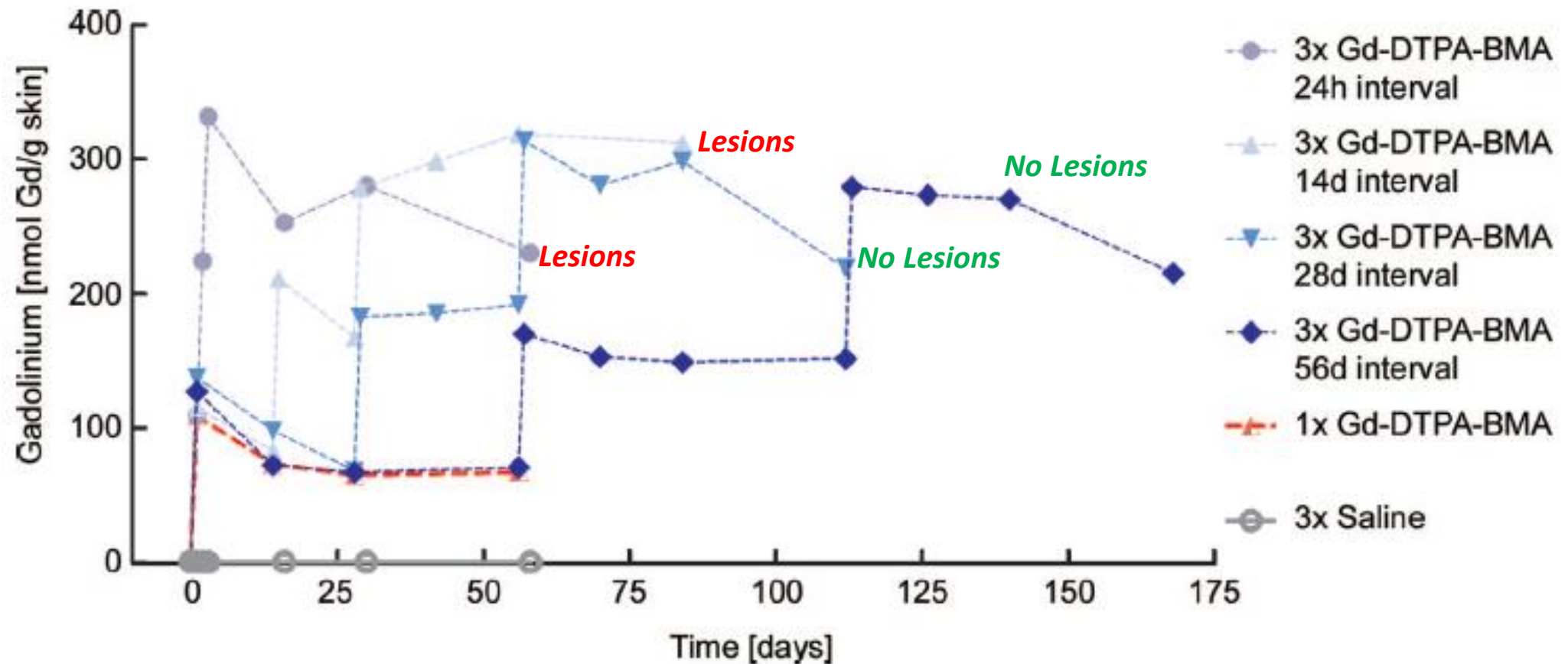
Skin lesions resolve with no or less frequent dosing



Skin lesions dependent on the injection interval and not on the amount of Gd in tissue.

“the skin lesions resolved during the experimental phase, although the Gd concentration in the skin further increased due the continued Gd-DTPA-BMA injections.”⁵

Skin lesions: Acute response unrelated to Gd retention



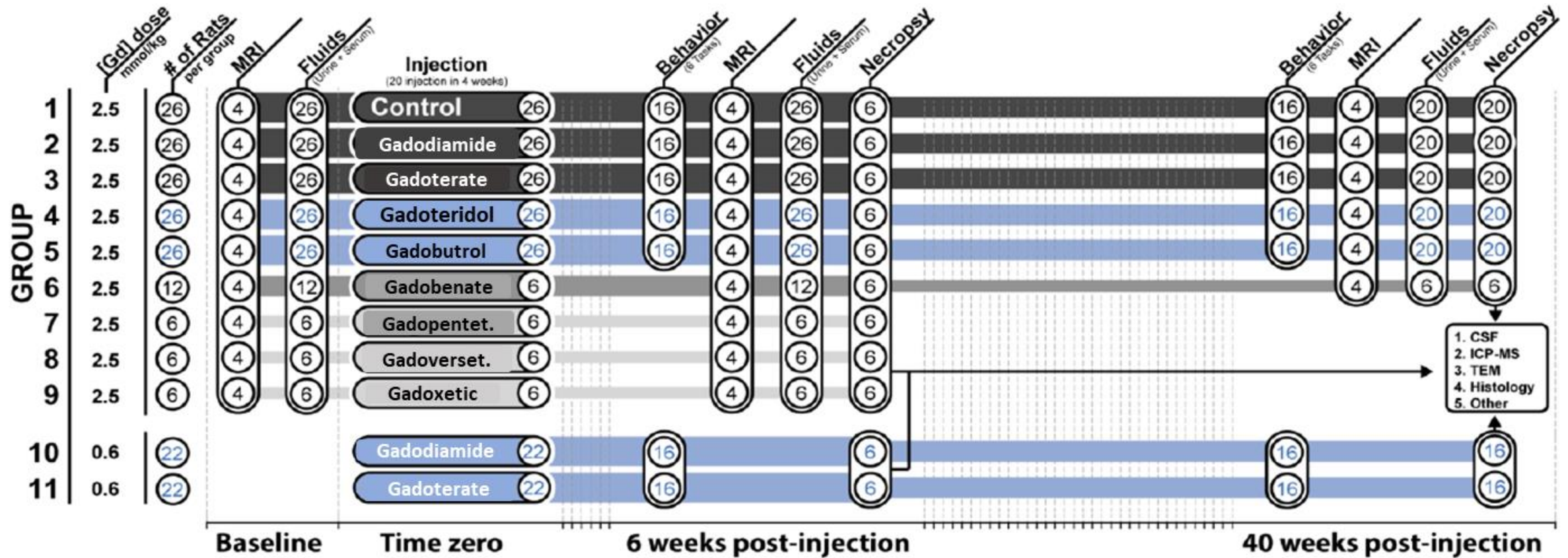
Behavioural Effects

- **Adult animals**
 - **Juvenile animals**
 - **In utero exposure**
-

Behavioural Effects – Adult Animals

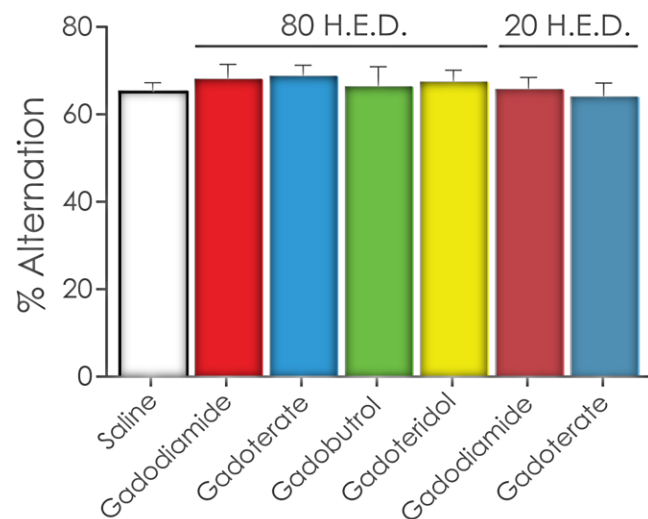
- During drug registration the potential for neurological effects of GBCAs were investigated in acute studies (e.g. single dose, Irwin test observations up to 24 hours).
 - Mid- to long-term Gd retention and the potential for associated neurological effects were not investigated
 - Since the more recent observations of Gd retention in the brain, long-term studies in adult animals have been initiated
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Mayo Clinic long-term study of rat behaviour

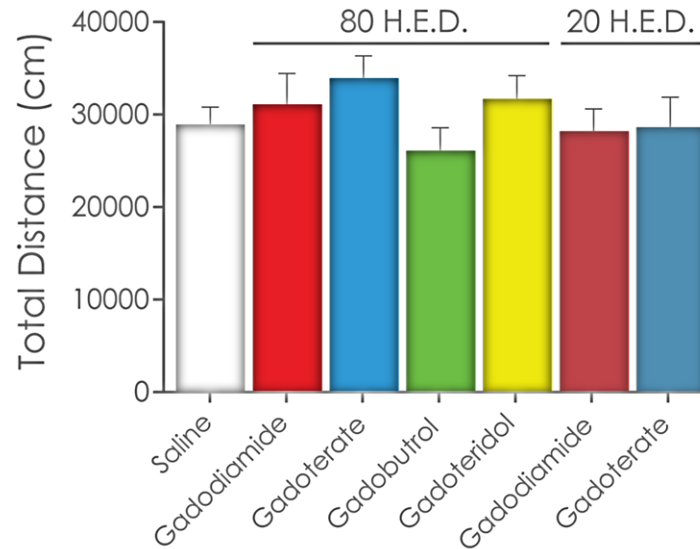


Mayo Clinic Rat Study: Preliminary data @6 weeks

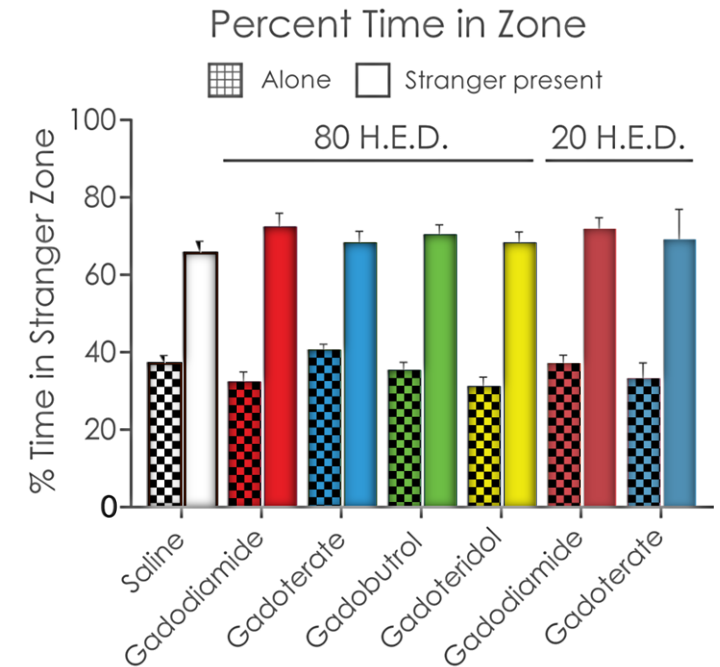
Y MAZE SPONTANEOUS ALTERNATION TEST



OPEN FIELD ARENA



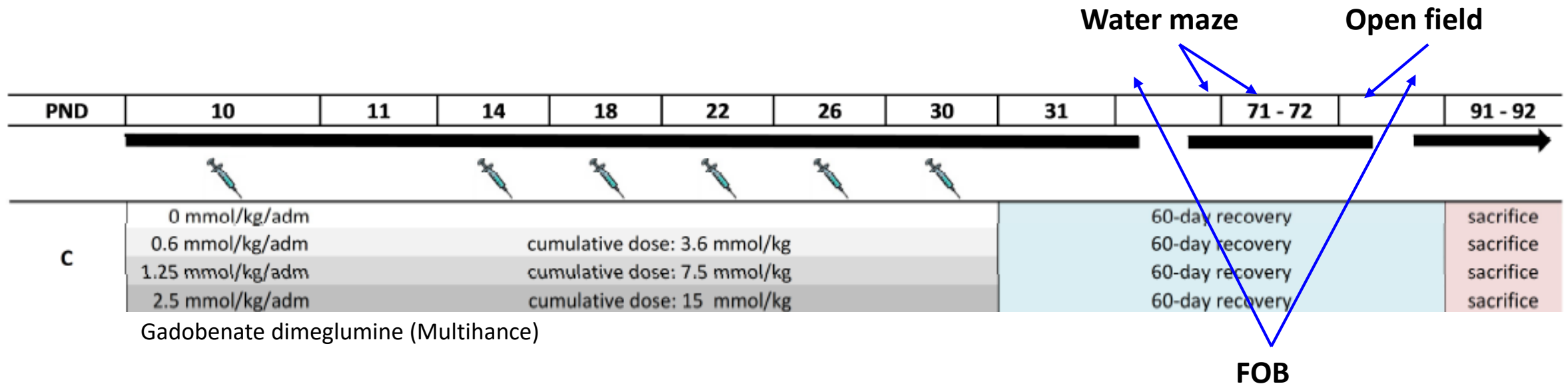
SOCIAL ANXIETY TASK



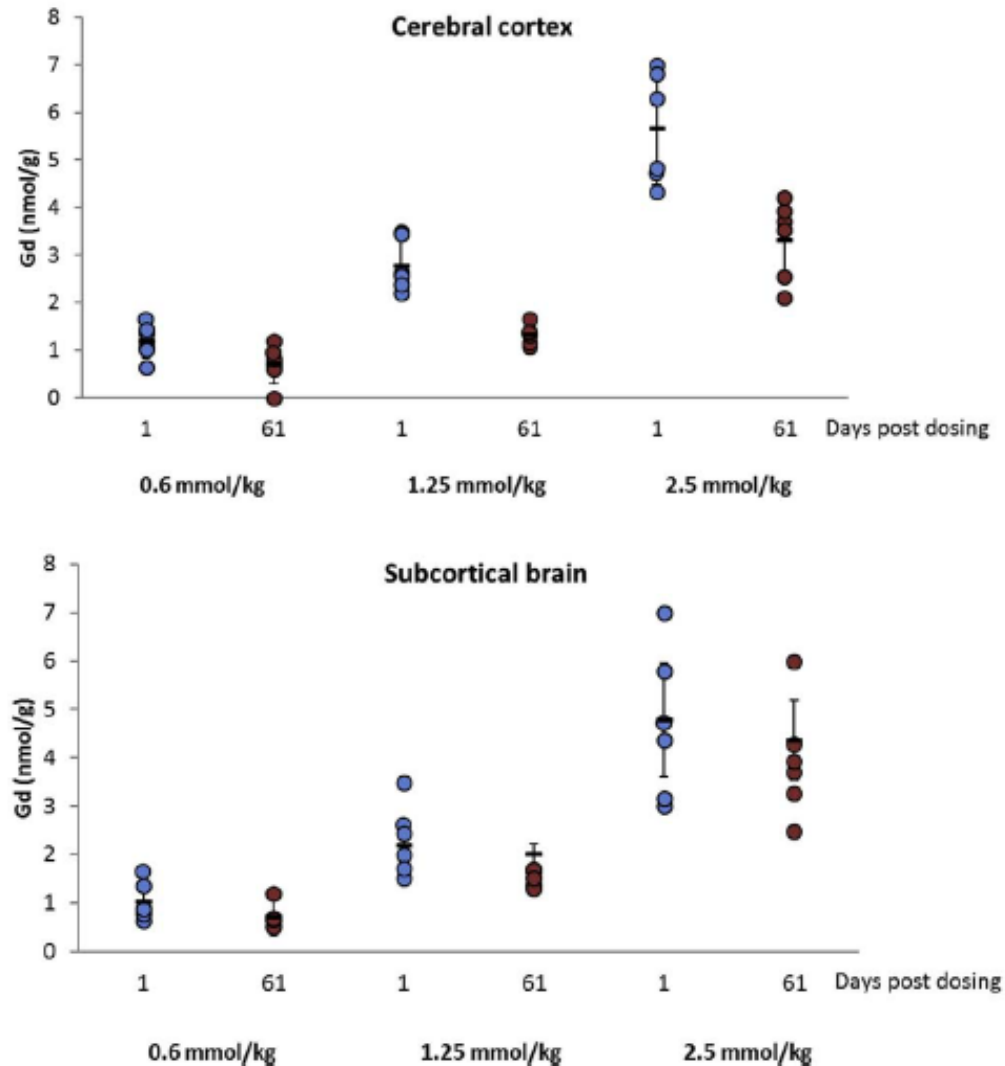
No effect on tests of memory, locomotor activity or anxiety

Behavioural Effects – Juvenile Animals

- In the last 5 years some companies have performed juvenile animal studies as a requirement to expand US indications to paediatric patients younger than 2 years of age



Adult rat behaviour after juvenile exposure



Gd was detected in the brain 60 days post-dosing with gadobenate dimeglumine (Multihance)
No effect on water maze, open-field test, & functional observation battery (with grip strength measurement, gait, pupillary & auditory reflex)

Behaviour after juvenile exposure

- A similar study on gadoterate meglumine (Dotarem) was published in 2015
- Brain Gd not measured, Gd detected in the liver & bone of a few high dose rats and in the kidneys at 60 days recovery
- No effect on behaviour:
Gripping reflex PND17
Papillary/Auditory PND21
Watermaze PND 38 & 45
Open Field PND 52

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journal homepage: www.elsevier.com/locate/yrtph



Non-clinical safety assessment of gadoterate meglumine (Dotarem[®])
in neonatal and juvenile rats



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In utero exposure – Drug registration studies

Teratogenicity

- **Potential teratogenic effects assessed by dosing pregnant animals (usually rats & rabbits) during organogenesis**
- **In general no specific teratogenic effects attributed to GBCA exposure**

Developmental

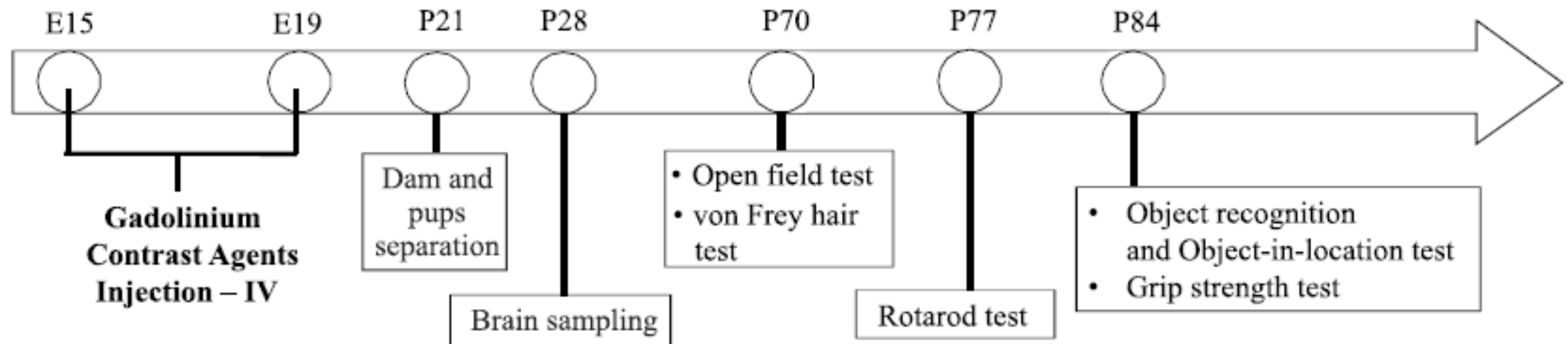
- **Peri- & post-natal studies in rats performed to examine potential effects on F1 generation**
 - **Daily dosing from GD 6 or 16 to PND 21. At PND 30 to 60 selected behavioural tests such as open field test and water maze. No specific effects attributed to GBCA exposure.**
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In utero exposure – Recent publication 2017/18

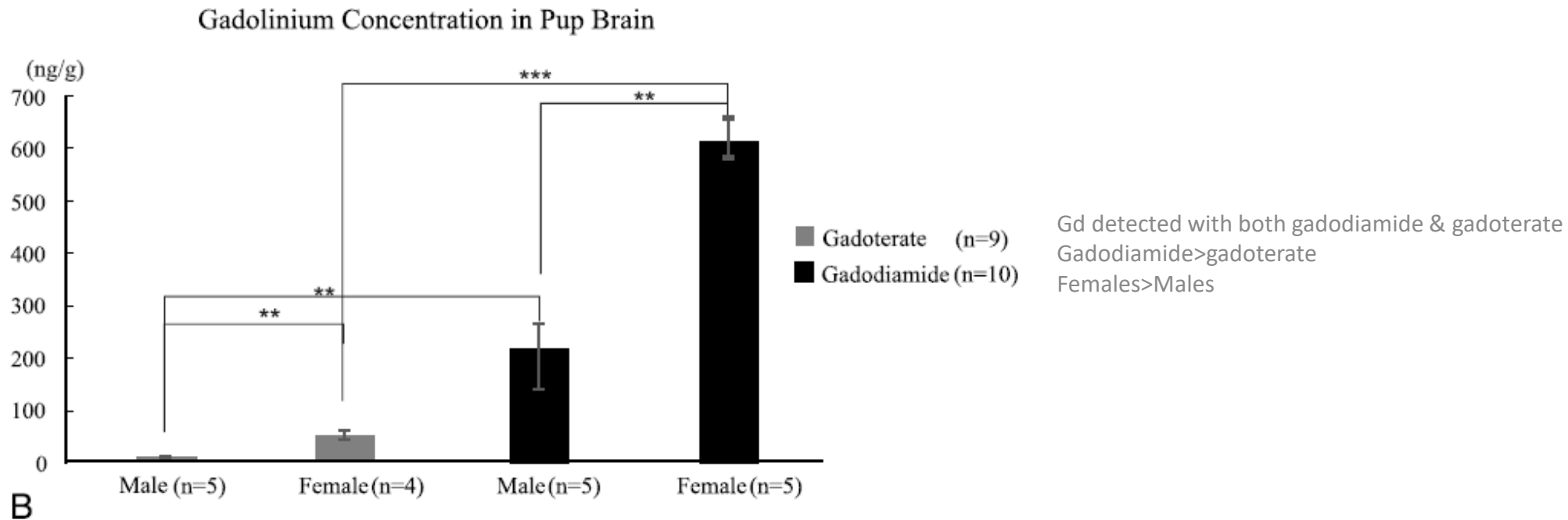
ORIGINAL ARTICLE

The Effect of Perinatal Gadolinium-Based Contrast Agents on Adult Mice Behavior

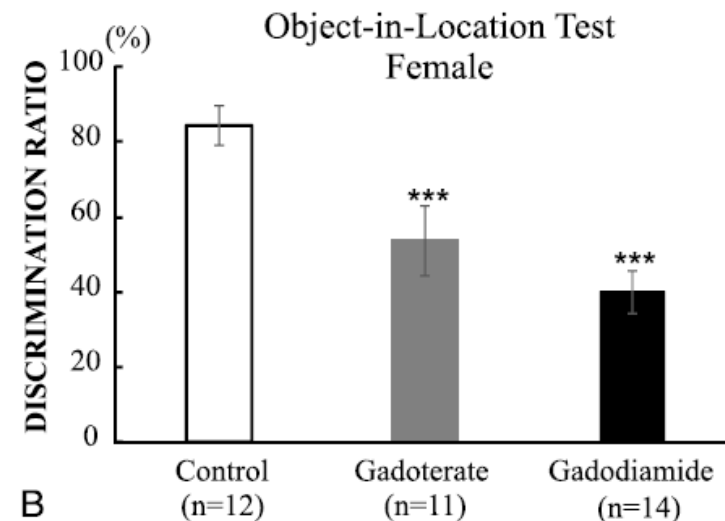
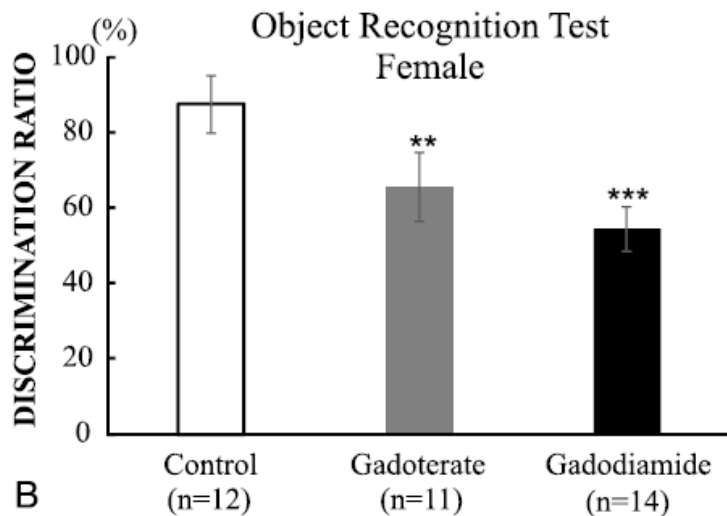
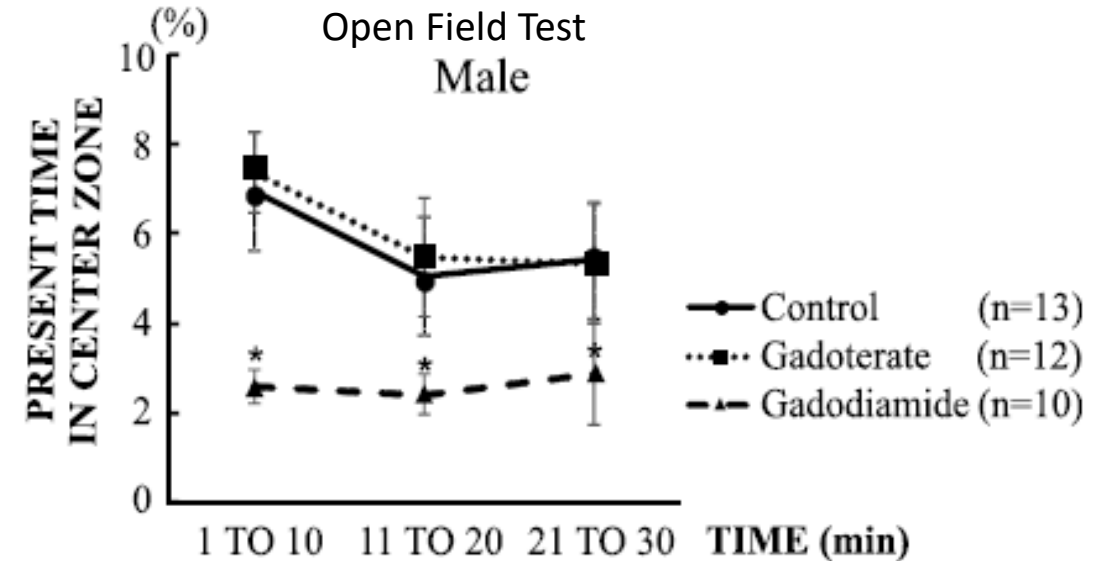
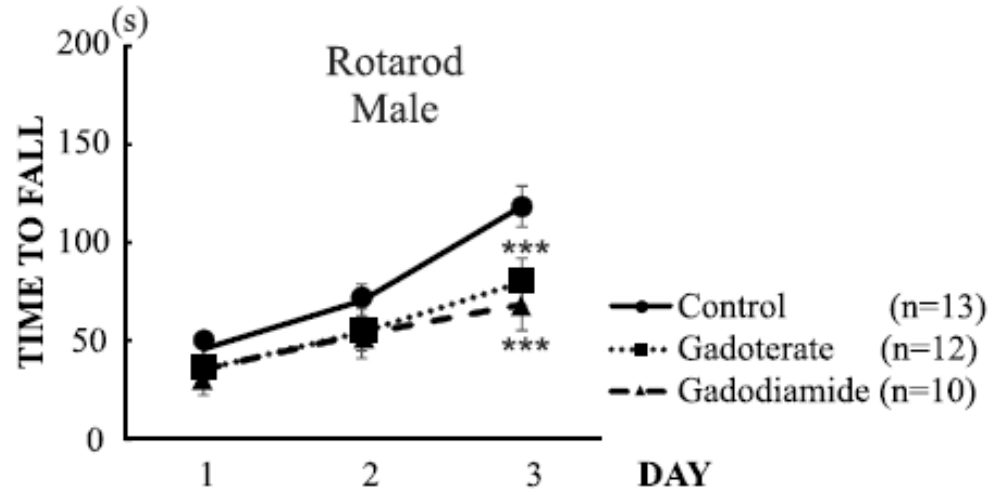
Miski Aghnia Khairinisa, MBIomedSc,† Yusuke Takatsuru, MD,* Izuki Amano, MD,*
Khongorzul Erdene, MD,‡ Takahito Nakajima, MD,‡ Satomi Kameo, PhD,§ Hiroshi Koyama, MD,§
Yoshito Tsushima, MD,‡|| and Noriyuki Koibuchi, MD, PhD**



Brain Gd detected in pup brain on PND 28



Various effects reported in 6 behavioural tests



Khairinisa et al. 2018 – Summary of results

		Open Field Travel Distance	Open Field Time in Centre	Rotarod	Object recognition	Object in location	Von Frey hair	Grip strength
Gadodiamide	Male	N	Y	Y	Y	Y	Y	Y
	Female	Y	Y	Y	Y	Y	N	Y
Gadoterate	Male	N	N	Y	N	Y	Y	Y
	Female	N	N	Y	Y	Y	N	N

Statistically significant effect	Y
No effect	N

Perinatal exposure to gadodiamide or gadoterate induced behavioural changes in adult mice. Gadodiamide>Gadoterate

Summary

- **Skin lesions in male rats are an acute response & unrelated to Gd retention**
 - **Behavioural studies following long-term Gd retention in adult rats are ongoing & will fill a knowledge gap**
 - **Juvenile rat studies with some GBCAs have shown no behavioural effects**
 - **Recent study of perinatal exposure reported behavioural effects in adult mice**
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Animal Clinical/Behavioural – Knowledge Gaps

Adult animals:	Data on potential long-term effects
Juvenile animals:	Not all GBCAs have been studied Additional adult testing e.g. rotarod
Peri-/Post-natal:	Historical data in rats - selected tests Single mouse study - not all GBCAs
Studies in rodents:	Relevance to human
