Critères de choix de l'utilisation du sévoflurane en anesthésie des animaux utilisés à des fins scientifiques

Ismael DAHER, PhD
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Équipements pour la recherche scientifique et préclinique

AFSTAL 2023
47e Colloque Afstal
Du 7 au 9 juin 2023 - BORDEAUX

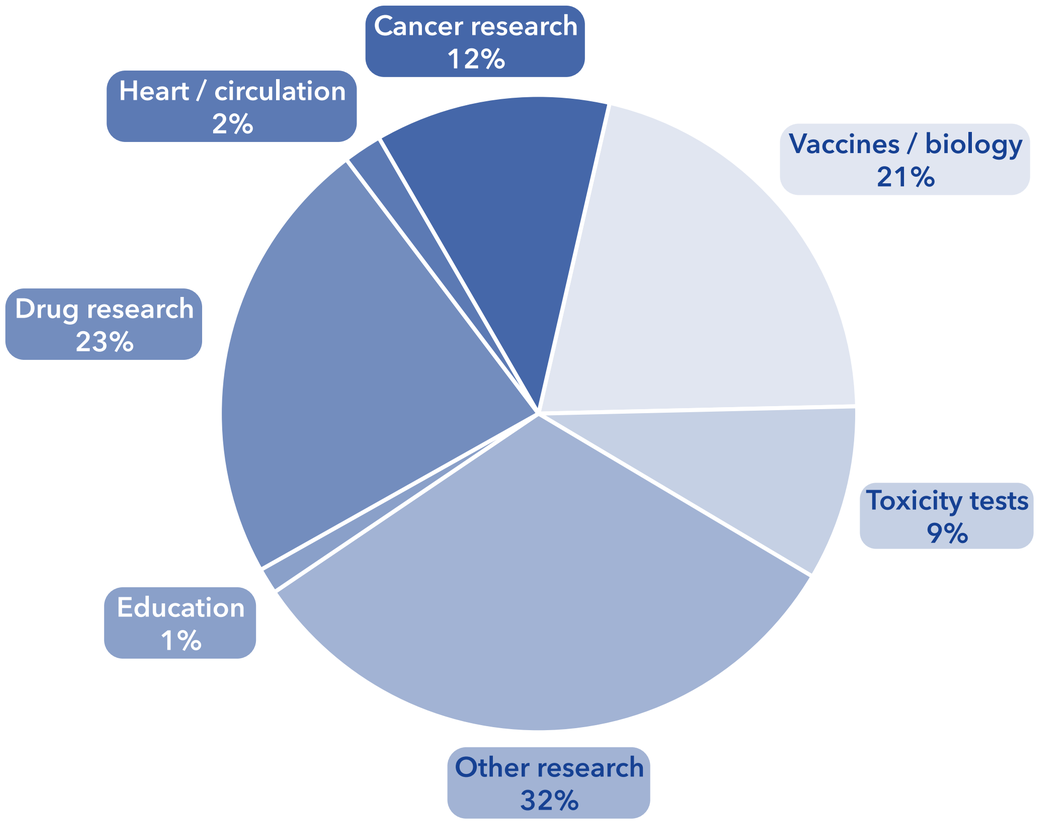
Anesthesia use for experimentation

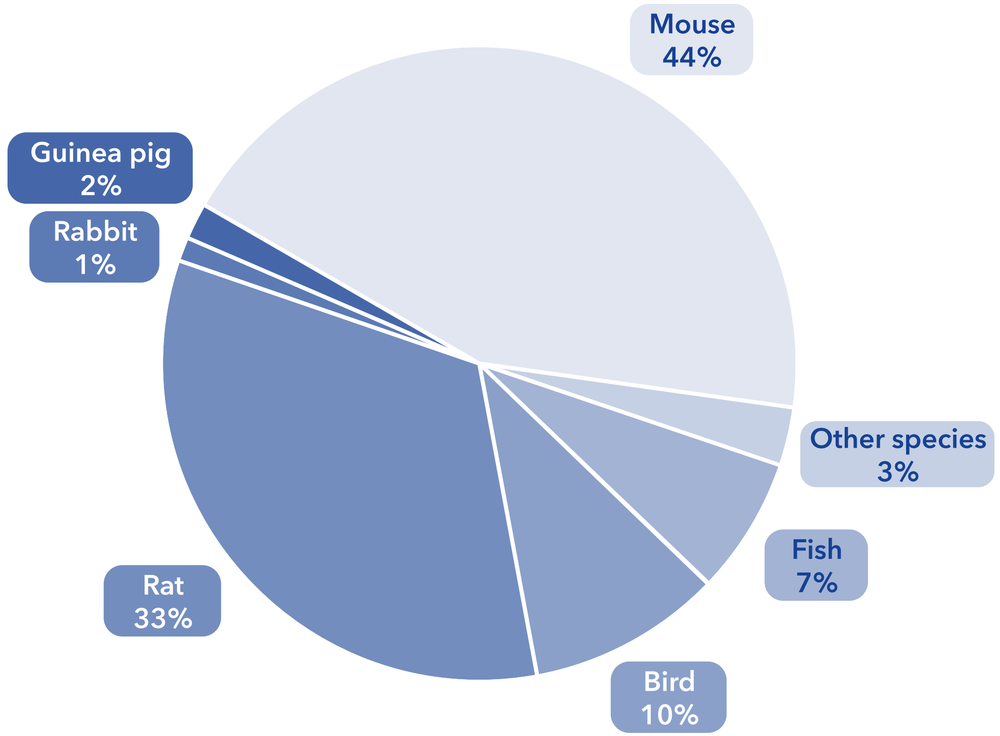
Directive 2010/63/EU

- **European Union** (EU) legislation "on the protection of animals used for scientific purposes“
- One of the most stringent ethical and welfare **standards worldwide**
- Became **formally applied** across the EU on January 1st 2013
- **Protects live non-human vertebrates** including independently feeding larval forms and foetal forms of mammals from the last third of their normal development, and live cephalopods

DIRECTIVE 2010/63/EU OF THE EUROPE PARLIAMENT AND OF THE COUNCIL
of september 2010
on the protection of animals use for scientific purposes
(Text with EEA relevance)

Anesthesia use for experimentation





Anesthesia use for experimentation

- Each person using an animal in an experiment must recognize when the animal is suffering, and reduce the pain

Decree 87-848, 19 October 1987 in France

- Keep away from interferences that can modify the results

- The type of procedure: some only need a handling, while others must be done under artifical ventilation

Anesthesia use for experimentation

Isoflurane

Ketamine

Stage 1	Also known as induction. Anesthesia has not yet taken effect, which means that the animal is still conscious and can feel pain
Stage 2	The excitement stage, follows the loss of consciousness. Involves erratic breathing, an irregular heart rate, and nausea as well as dilation of the pupils
Stage 3	Stage III is known as surgical anesthesia The muscles relax, breathing slows, and eye movement slows to a stop
Stage 4	Also known as overdose. In this stage, the animal has received an excess of medication. Suppresses activity in the medulla or brain stem, and in turn the animal's cardiovascular and respiratory systems fail

Anesthesia use for experimentation

	Behavior	Respiration	Cardiovascular Function	Response to Surgery	Depth	Eyeball Position	Pupil Size	Pupillary Light response	Muscle Tone	Reflex Response
Stage I	Disoriented	Normal, may be panting RR 20-30 bpm	HR unchanged Hypertension	Struggle	Not anesthetized	Central	Normal	Yes	Good	All present
Stage II excitatory stage	Excitement struggling vocalization	Irregular, may hold breath or hyperventilate	HR may increase, hypertension	Struggle	Not anesthetized	Central, possible nystagmus	Yes	Yes	Good	All present, may be exaggerated
Stage III, Plane 1, light anesthesia	Anesthetized	Regular RR 12-20 bpm	Pulse strong HR > 90 bpm Normal BP	May respond with movement	Light	Central or rotated, may be nystagmus	Normal	Yes	Good	Swallowing poor or absent, good others present but diminished
Stage III, Plane 2, surgical anesthesia	Anesthetized	Regular, may be shallow RR 12-16 bpm	HR > 90 bpm Increasing hypotension	HR and RR may increase	Moderate	Often rotated ventrally	Slightly dilated	Sluggish	Relaxed	Patellar, ear flick, palpebral, relaxed and corneal may be present (but diminished), others absent
Stage III, Plane 3, deep anesthesia	Anesthetized	Shallow RR <12 bpm	HR 60-90 bpm CRT increased, pulse less strong, increasing hypotension	None	Deep	Usually central, may rotate ventrally	Moderately dilated	Very sluggish or absent	Greatly reduced	All reflexes diminished or absent
Stage III, Plane 4	Anesthetized	Jerky	HR < 60 bpm Prolonged CRT, pale mm Significant Hypotension	None	Overdose	Central	Widely dilated	Unresponsive	Flaccid	No reflex activity
Stage IV	Moribund	Apnea	Cardiovascular collapse	None	Dying	Central	Widely dilated	Unresponsive	Flaccid	No reflex activity

Anesthesia use for experimentation

Basic reflexes in rodents, their method of assessment, and significance in anesthetic monitoring

Reflex	Method of assessment	Significance
Righting reflex	The animal is gently rolled onto its back. The righting reflex is lost when the animal is unable to regain an upright posture (standing or lying down).	Loss of the righting reflex (LORR) is correlated with a loss of consciousness.
Skin pinch reflex (panniculus reflex)	The loose skin over the animal's dorsal surface is pinched. This reflex is lost when the animal does not visibly respond (e.g by flinching).	Loss of this response is correlated with loss of superficial pain.
Toe pinch reflex (pedal withdrawal reflex)	One of the hind limbs is gently extended, and then the footpad is firmly pinched. The toe pinch reflex is lost when the animal does not respond by withdrawing the extended limb.	Loss of this reflex is correlated with loss of deep pain.

Measures of anesthetic depth in rodents under isoflurane anesthesia

Too light	Appropriate		Too deep
	Light plane of anesthesia	Deep plane of anesthesia	
Loss of the righting reflex (LORR) but muscle tone is still present Reflexes present Rapid and shallow respiratory rate	Muscle tone loose/weak Skin pinch reflex absent Toe pinch reflex variably present Rhythmic, but shallow, respiratory rate	Muscle tone loose/weak Skin pinch reflex absent Toe pinch reflex absent Reduced respiratory rate, but still rhythmic	Muscle tone loose/weak Skin pinch reflex absent Toe pinch reflex absent Respiratory rate may be erratic, abdominal breathing has developed ("see-saw"breathing)

Anesthesia use for experimentation

MAC : minimum alveolar concentration where 50% of animals lose a motor response to a noxious stimulus. The lower the MAC value, the lower the concentration required, ie the more potent the anesthetic.

CNS function lost	Plane of anesthesia	Statuts of CNS functions	Approximate MAC value
Loss of memory	Unable to form memories	Cerebral functions, spinal and autonomic reflexes intact	0.25
Loss of consciousness	Unable to perceive pain	Cerebral functions anesthetized; spinal and autonomic reflexes intact	0.5
Loss of motor response to a noxious stimulus	No motor response; surgical plane of anesthesia	Cerebral functions and spinal reflexes anesthetized;	1.0
Blunted autonomic reflexes	Autonomic nervous system is not responsive to physiologic	Cerebral functions, spinal ref lexes, and autonomic ref	1.5

Anesthesia use for experimentation

Use of gaseous anesthesia vs injectable anesthesia

	Anesthetic Protocol	Route of Administration
Anesthetic protocols for immobilization or imaging	Ketamine 80-100 mg/kg Xylazine 8-10 mg/kg	IP
	Ketamine 100 mg/kg Xylazine 10 mg/kg Carprofen 4 mg/kg	
	Ketamine 100 mg/kg Xylazine 10 mg/kg Buprenorphine 0.3 mg/kg	
	Tribromoethanol250-300 mg/kg	
Anesthetic protocols for surgical plane	Ketamine 80-100 mg/kg Xylazine 8-20 mg/kg Acepromazine 1-3 mg/kg	
	Males: Alfaxalone 80-120 mg/kg Xylazine 10 mg/kg Females: Alfaxalone 40-80 mg/kg Xylazine 10 mg/kg	IP if NOT doing a laparotomy or entering peritoneal cavity SQ if doing a laparotomy or entering the peritoneal cavity
	Alfaxalone30-60 mg/kg Medetomidine0.5-0.75 mg/kg Butorphanol5 mg/kg	SQ
	Medetomidine0.3 mg/kg Midazolam 4 mg/kg Butorphanol 5 mg/kg	IP
	Tribromoethanol250-500 mg/kg	

Anesthesia use for experimentation

Ether	Halothane	Isoflurane	Enflurane	Sevoflurane	Metoxiflurane
Highly soluble, low induction; causes irritation in the eyes, nose and airways; risk of explosion	Rapid induction; efficacious for euthanasia; high potential for hepatotoxicity	Lower solubility than halothane, but faster induction; unpleasant smell; small hepatotoxicity	Lower potency than halothane; efficacious for euthanasia, linked to scattered convulsions; potential for hepatotoxicity	Less potent than halothane and isoflurane, as well as lower vapour pressure	Highly soluble; slow induction; potential for nephrotoxicity

- ✔ Fast action and recovery low blood solubility
- ✔ Few effects on the cardiovascular functions and the cerebral blood flow halothane
- ✔ Easy anesthesia depth control

- ✖ Not an analgesic
- ✖ Respiratory issues, pulmonary tract inflammation
- ✖ Central hypothermia
- ✖ Liver toxicity cited in several studies

Isoflurane VS Sevoflurane

Several factors have to be considered when choosing an anesthetic

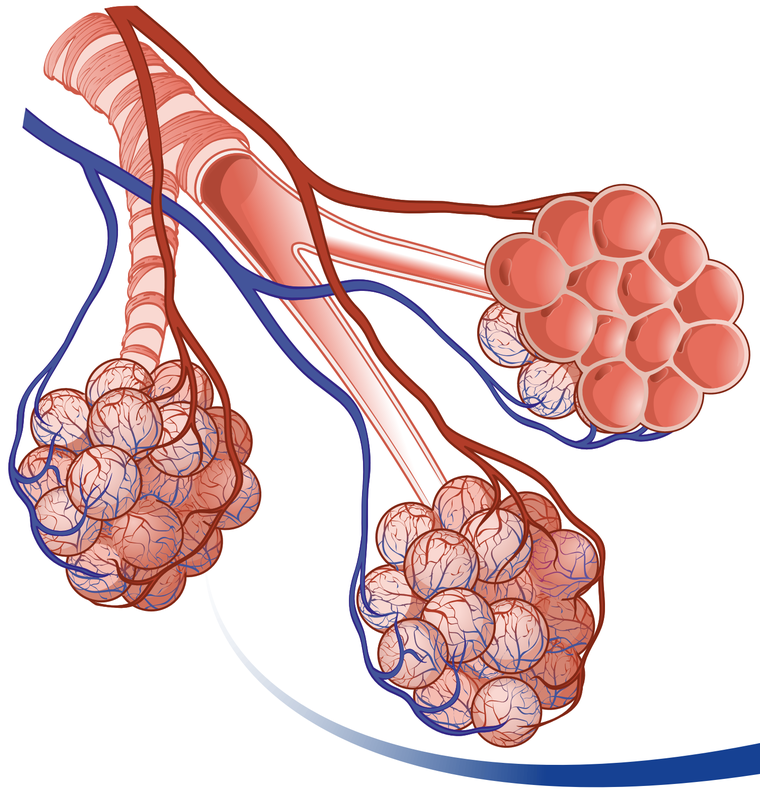
- **The animal species, strain and eventually the animal temperament:** a well-known example is the observed shock in guinea pigs when using ether
- **The animal well-being:** some short procedures with little pain only require using a light anesthetic
- **The surgical procedure:** duration, light or deep surgery, imaging etc...
- **The means and experience of the person:** using an injectable anesthetic can be safer for without experience with volatile agents
- **The animal and user safety**

Isoflurane VS Sevoflurane

	Isoflurane	Sevoflurane
Minimum alveolar concentration MAC	1.3	2.4
Blood-gas solubility	Higher	Lower, thus achieving a rapid effect in the brain
Induction and recovery	Lower	Faster
Anaesthetic depth	Good	Faster change in depth
Tolerance	Can induce irritation	Less airway irritation
Use with soda lime	x	Produces compound A
Imaging in rodents	Optimal	-
Smell	Strong and pungent	Sweet
Anesthesia side effects	Same	Same
Safety	x	Xx
Cost	+	Higher x12 at similar gas flow
Consumption	Lower	Higher because surgical anesthesia achieved at 1.5xMAC

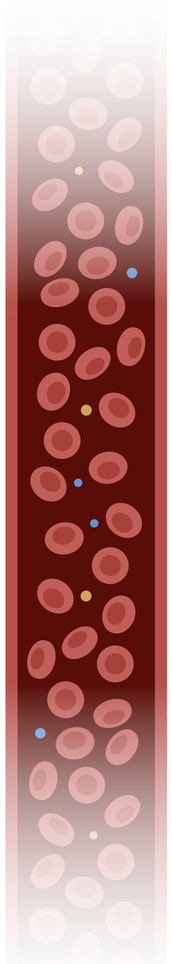
Isoflurane VS Sevoflurane

	Blood / gas partition coefficient
Halothane	2.30
Enflurane	1.80
Isoflurane	1.41
Desflurane	0.42
Sevoflurane	0.69

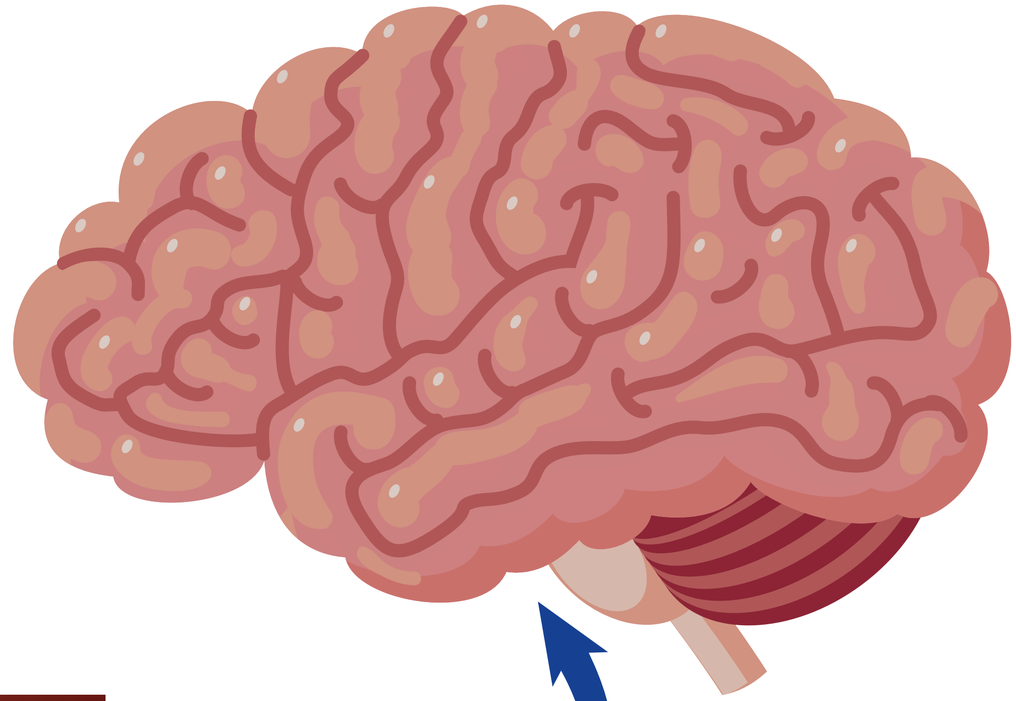


ALVEOLI

Low gas sollubility



BRAIN **Higher brain concentration**



BLOOD VESSEL

Decrease sollubility in blood

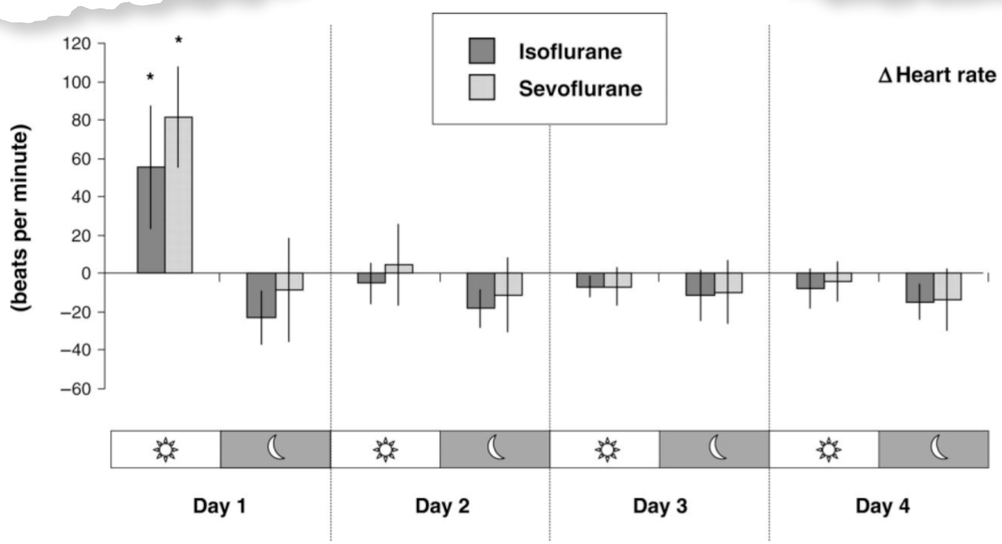
Isoflurane VS Sevoflurane

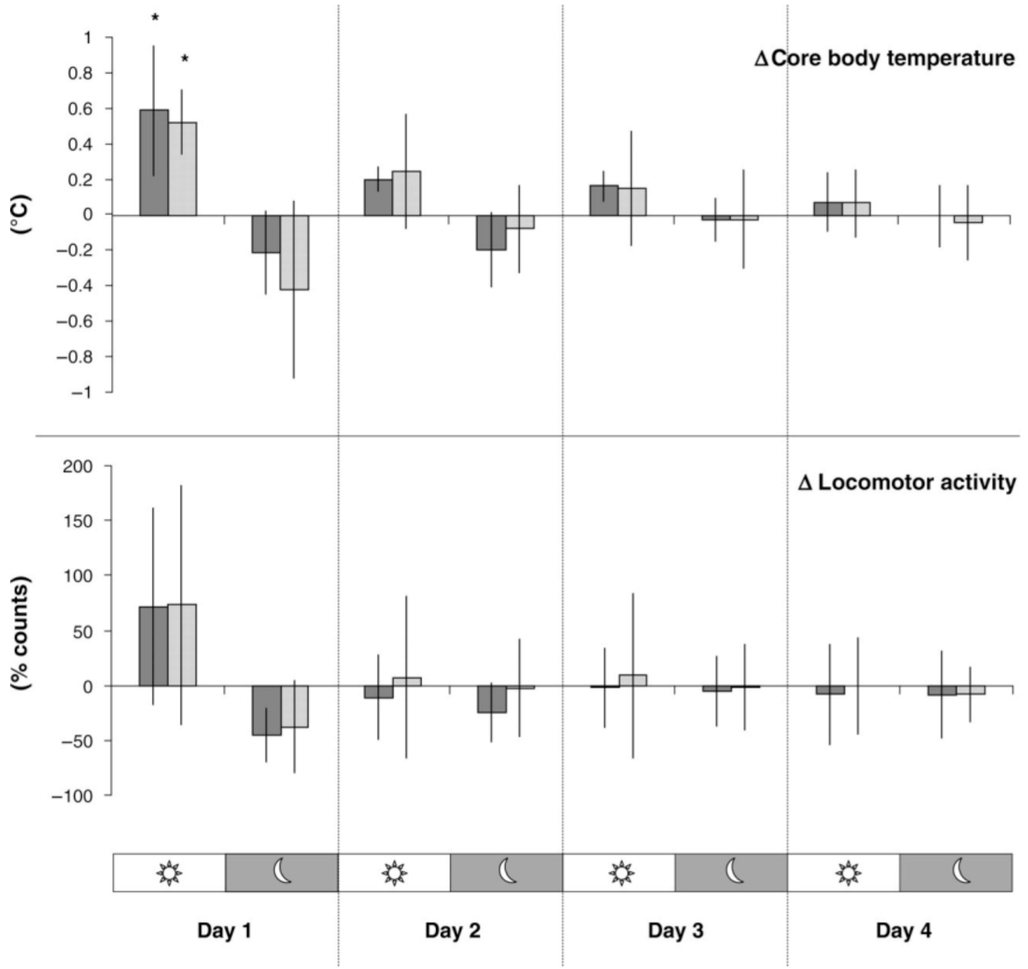
Locomotor activity, daily food and water consumption and body weight progression showed no abnormalities after anaesthesia

Comparative Study > Lab Anim. 2010 Oct;44(4):329-36. doi: 10.1258/la.2010.009085. Epub 2010 May 27.

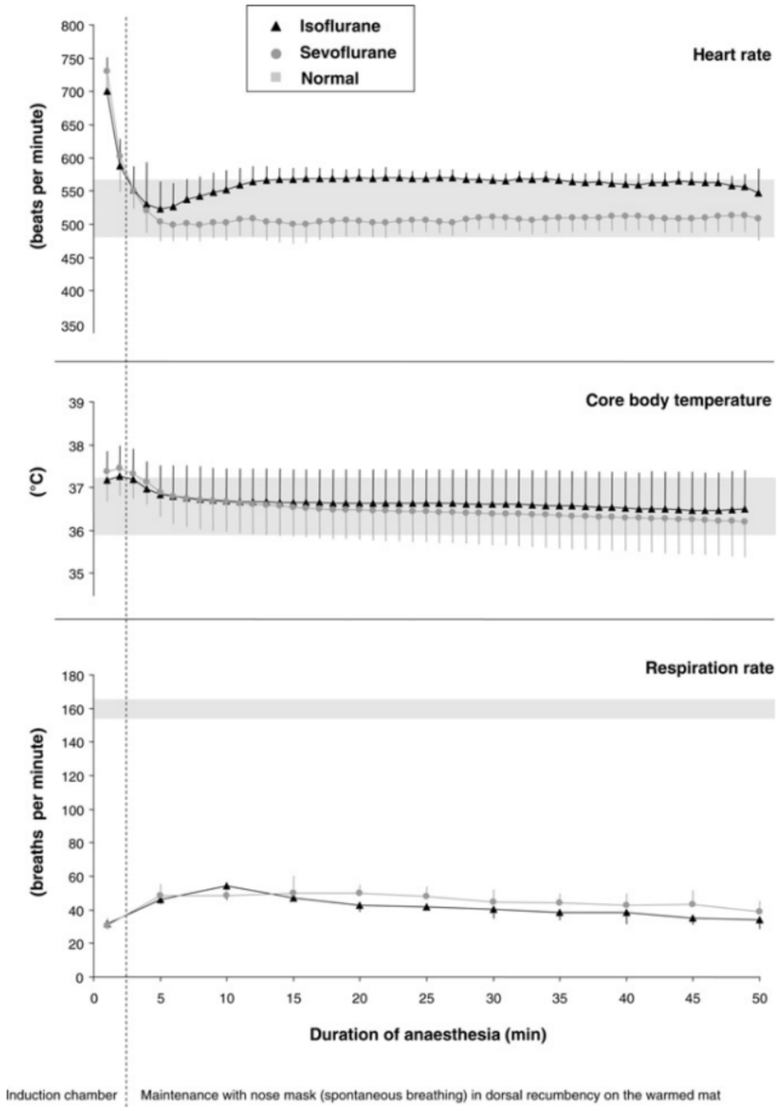
Isoflurane and sevoflurane provide equally effective anaesthesia in laboratory mice

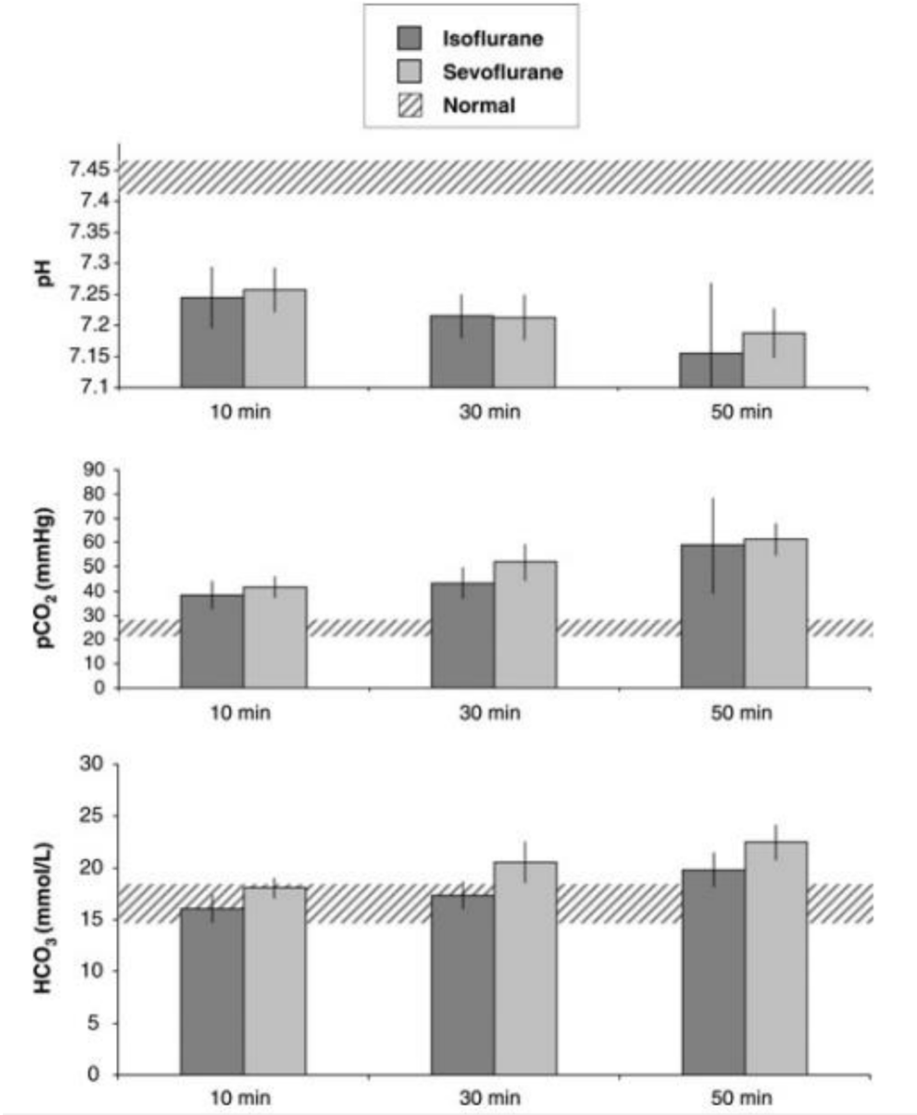
Nikola Cesarovic [1], Flora Nicholls, Andreas Rettich, Peter Kronen, Michael Hässig, Paulin Jirkof, Margarete Arras



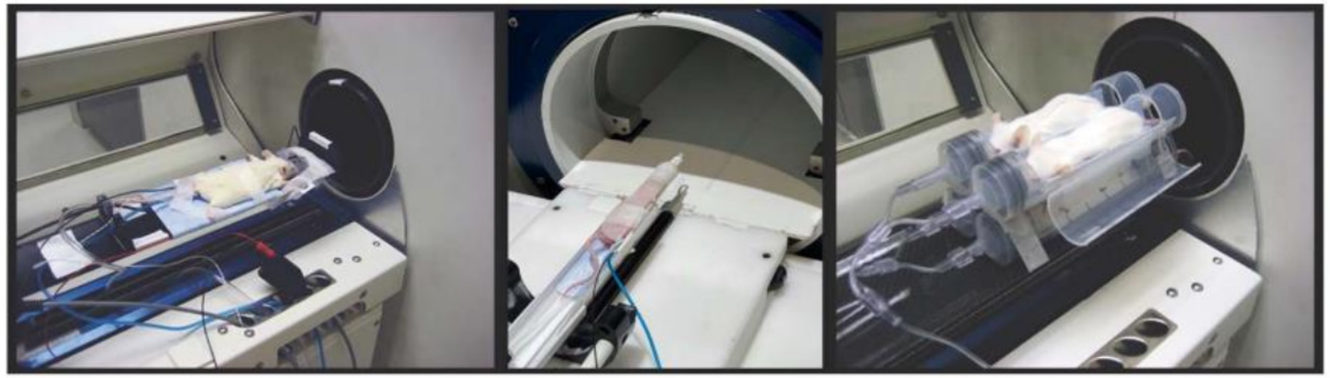


Isoflurane VS Sevoflurane





Isoflurane VS Sevoflurane



RED – Contraindicated with high physiological interference regarding tracer uptake and biodistribution

ORANGE

- Increased safety risk to animal with possibility of mortality
- Moderate interference with tracer uptake

GREEN - Low interference with physiological processes and expected tracer uptake

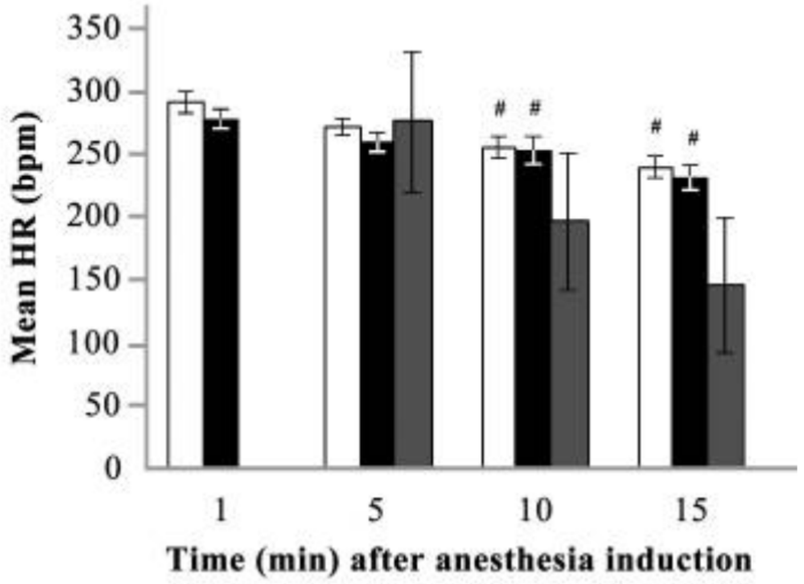
Table 1: Compatibility of various anaesthetic agents for optimal microPET/CT imaging of indicated radiotracers

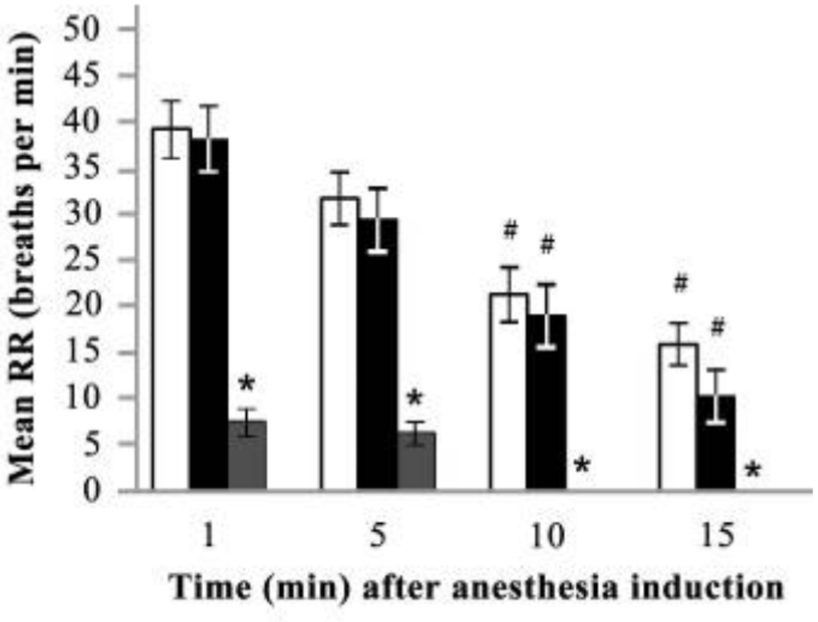
		[^{18}F]FDG	[^{68}]Ga-DOTA-TATE	[^{68}]Ga-PSMA11
Inhalation	Isoflurane			
	Sevoflurane			
Injectable	Ketamine/Xylazine			
	Pentobarbital			
	Propofol			
	Fentanylcitrate fluanisone / Diazepam		n/a	n/a

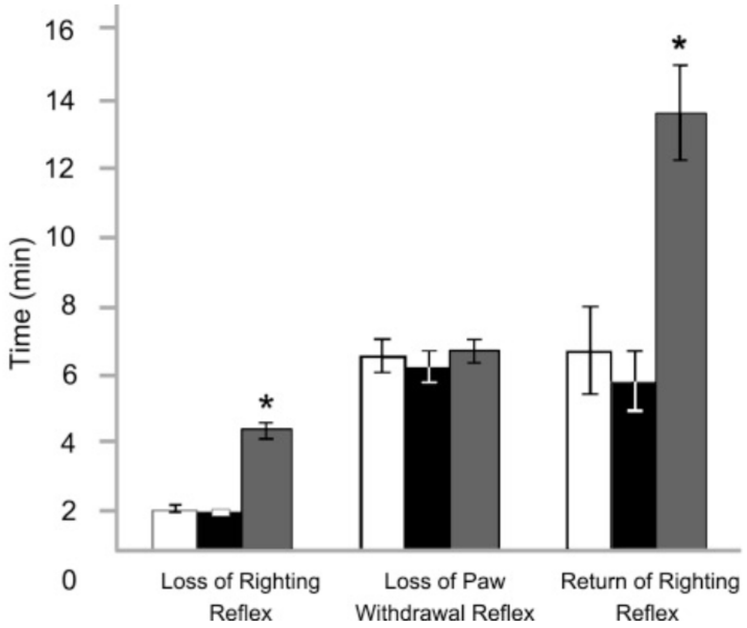
Isoflurane VS Sevoflurane

The Physiologic Effects of Isoflurane, Sevoflurane, and Hypothermia Used for Anesthesia in Neonatal Rats (*Rattus norvegicus*)

Monika K Huss,[1,*] Helen H Chum,[2] Angela G Chang,[1] Katechan Jampachairsi,[3] and Cholawat Pacharinsak[1]



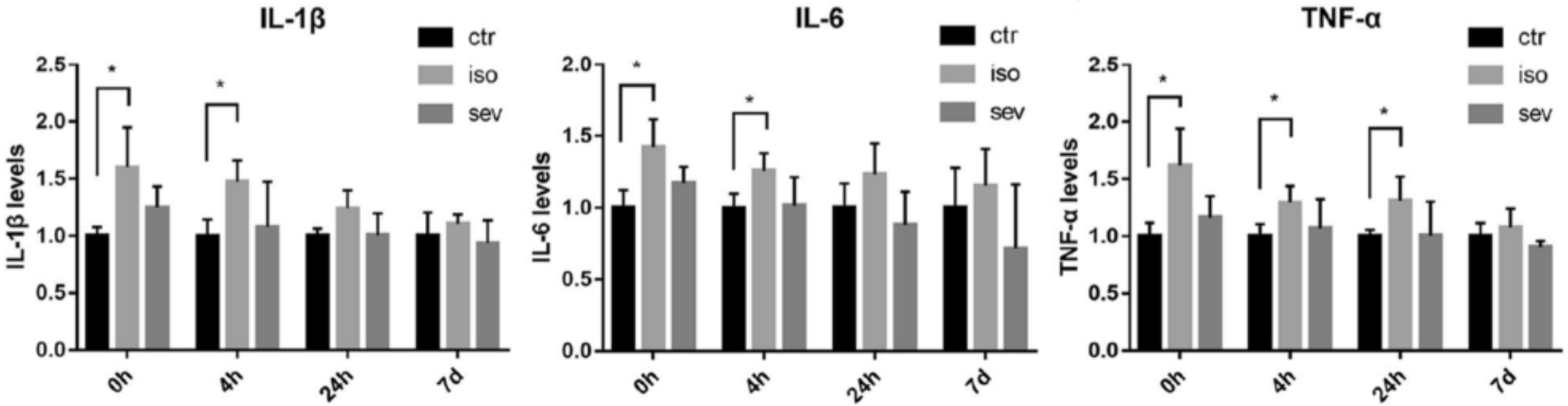




Isoflurane VS Sevoflurane

The differential effects of isoflurane and sevoflurane on neonatal mice

Shuai Zhao[1,4], Ziqi Fan[1,4], Jing Hu[1], Yueli Zhu[1,3], Caixiu Lin[1,2], Ting Shen[1], Zheyu Li[1], Kaicheng Li[1], Zhirong Liu[1], Yanxing Chen[1]✉ & Baorong Zhang[1]✉



Isoflurane VS Sevoflurane

Economic considerations in the use of inhaled anesthetic agents

JULIE GOLEMBIEWSKI

Am J Health-Syst Pharm—Vol 67 Apr 15, 2010 Suppl 4 | S9

Table 1.
Estimated Cost per MAC Hour ($) of Inhaled Anesthetic Agents[7,a,b]

Fresh Gas Flow Rate (L/min)	Isoflurane[c]	Desflurane[d]	Sevoflurane[e]
1	0.52	12.96	6.05
2	1.04	25.93	12.10
3	1.56	38.88	18.15

[a]MAC = minimum alveolar concentration.
[b]All estimated costs per MAC hour are based on a duration of 60 minutes and the following formula: Cost per MAC hour ($) = [(Concentration)(FGF)(duration)(MW)(cost/mL)]/[(2412)(D)] where FGF is fresh gas flow rate in L/min, MW = molecular weight in g, cost per mL is in dollars based on average wholesale price, and D = density in g/mL.
[c]Isoflurane calculations are based on a concentration of 1.15%, molecular weight (MW) of 184.5 g, cost per mL of $0.15, and density of 1.496 g/mL.
[d]Desflurane calculations are based on a concentration of 6%, MW of 168g, cost per mL of $0.96, and density of 1.45 g/mL.
[e]Sevoflurane calculations are based on a concentration of 2.05%, MW of 201g, cost per mL of $0.90, and density of 1.51 g/mL.

$$\text{Cost per MAC hour (\$)} = [(\text{Concentration})(\text{FGF})(\text{duration})(\text{MW})(\text{cost/mL})]/[(2412)(\text{D})]$$

Analgesia and association with anesthetics

Analgesia is a neurological state where pain is not perceived to its full ability. Painful stimuli are still present but not perceived as pain while the patient is still conscious

- It does become a factor during recovery and the smooth transition from anesthesia to analgesia
- Therefore, as the animal emerges from anesthesia to being able to perceive pain, analgesia will be present and will help bridge the animal to the full efficacy of the postoperative analgesic protocol
- These effects are absent for inhalant anesthetics, and the postoperative analgesic protocol must fully address pain from the instant the animal regains consciousness
- Analgesics can provide value during the surgical procedure when using inhalant anesthesia because they can decrease the amount of inhalant anesthesia, which is addressed below

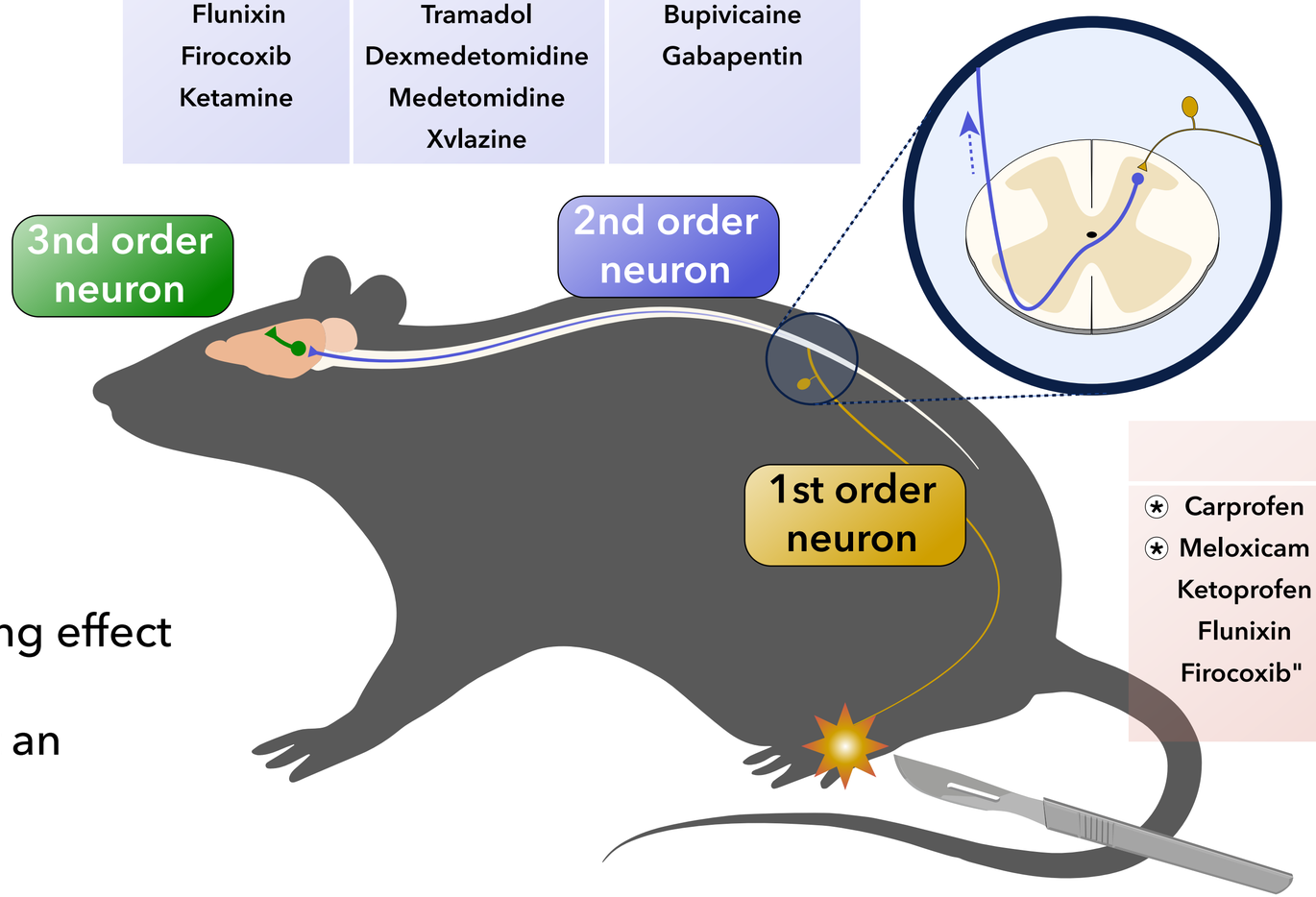
Analgesia and association with anesthetics

Modulation

⊛ Carprofen	⊛ Buprenorphine	Lidocaine
⊛ Meloxicam	Butorphanol	Bupivicaine
Ketoprofen	Morphine	Liposomal-Bupivicaine
Flunixin	Tramadol	Gabapentin
Firocoxib	Dexmedetomidine	
Ketamine	Medetomidine	
	Xylazine	

Perception

⊛ Buprenorphine	Dexmedetomidine
Butorphanol	Medetomidine
Morphine	Xylazine
Tramadol	Isoflurane/
	§ sevoflurane
	§ Acepromazine
	Ketamine



Transmission

Lidocaine
Bupivacaine
Liposomal-Bupivicaine

Transduction

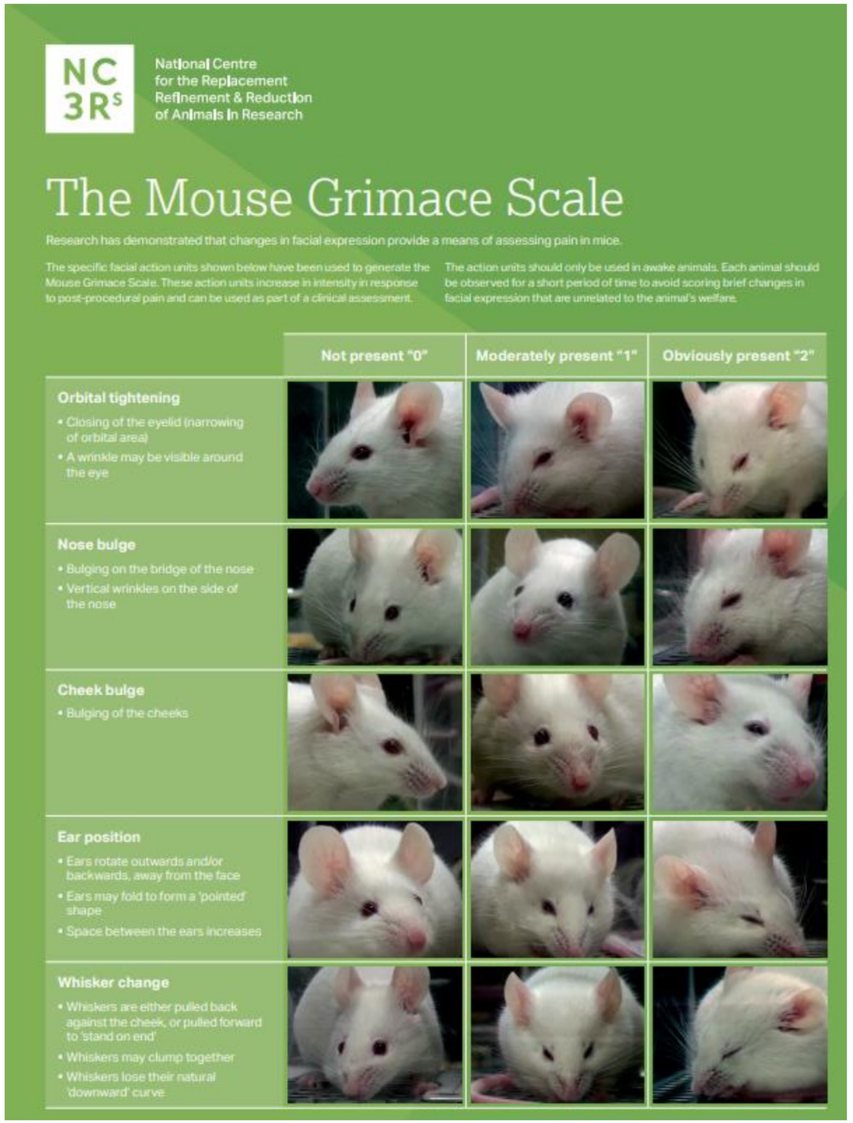
⊛ Carprofen	⊛ Buprenorphine	Liposomal-Bupivicaine
⊛ Meloxicam	Butorphanol	EMLA Cream
Ketoprofen	Morphine	Capsaicin Cream
Flunixin	Tramadol	Lidocaine
Firocoxib"		Bupivicaine

⊛ Indicates a long lasting effect
§ Suppresses the pain perception but is not an analgesic

Analgesia and association with anesthetics

Agent	Mouse			Rat		
	Dose (mg/kg)	Route	Frequency	Dose (mg/kg)	Route	Frequency
Buprenorphine	0.05-0.1	SC	6-12 h	0.01-0.1	SC, IM	8-12 h
Tramadol	5-40	SC, IP	ND	5-20	SC, IP	ND
Carprofen	2-5	SC	12-24 h	2-5	SC	24 h
Meloxicam	1-5	SC, PO	12 h	1-2	SC, PO	12-24 h
Ketoprofen	2-5	SC	24 h	2-5	SC	24 h
Acetaminophen	30-40	PO	ND	15	PO	ND
Agent	200	PO	ND	200	PO	ND

Analgesia and association with anesthetics



Grimace scale, burrowing, and nest building for the assessment of post-surgical pain in mice and rats—A systematic review

Katharina Aulehner, [1] Cathalijn Leenaars, [2] Verena Buchecker, [1] Helen Stirling, [1] Katharina Schönhoff, [1] Hannah King, [1] Christine Häger, [2] Ines Koska, [1,†] Paulin Jirkof, [3] André Bleich, [2] Marion Bankstahl, [2] and Heidrun Potschka [1,*]

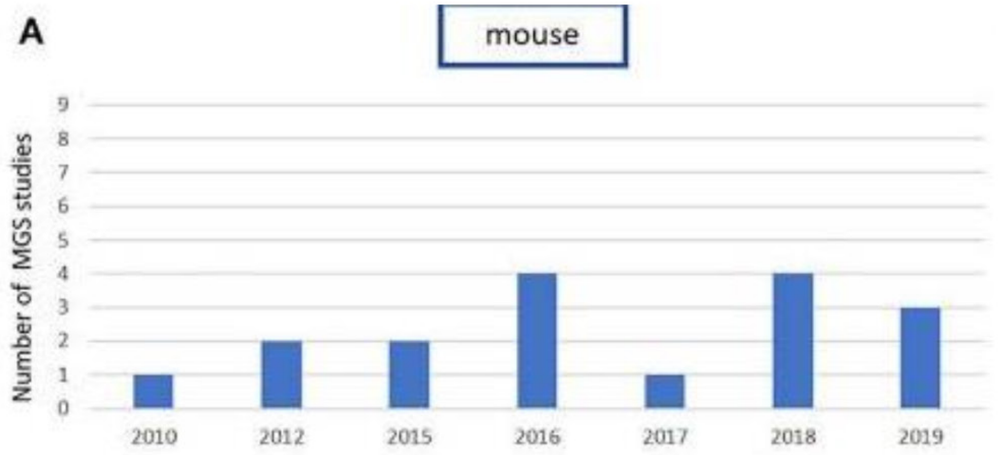
Real-time application of the Rat Grimace Scale as a welfare refinement in laboratory rats

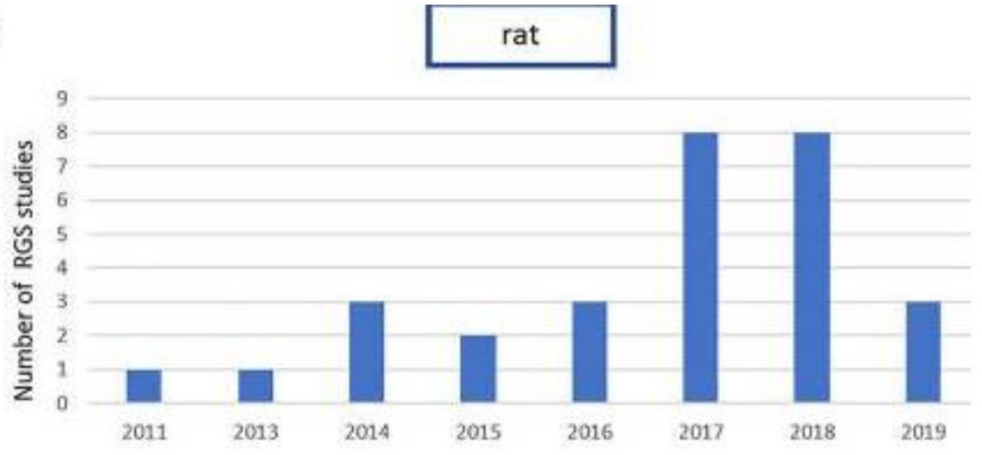
Vivian Leung, Emily Zhang & Daniel SJ Pang

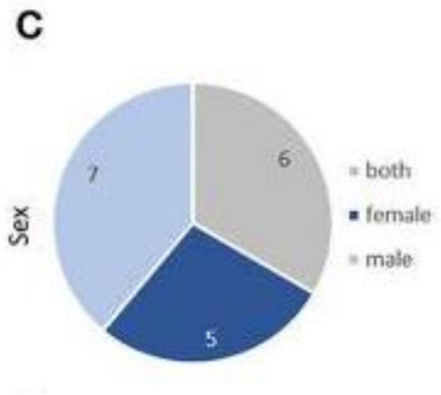
The development and use of facial grimace scales for pain measurement in animals

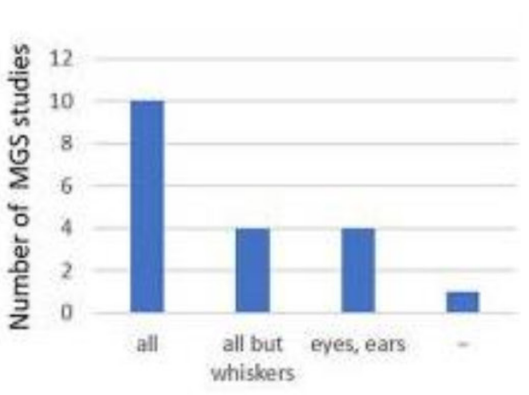
Jeffrey S. Mogil [a], Daniel S.J. Pang [b], Gabrielle Guanaes Silva Dutra [a], Christine T. Chambers [c]

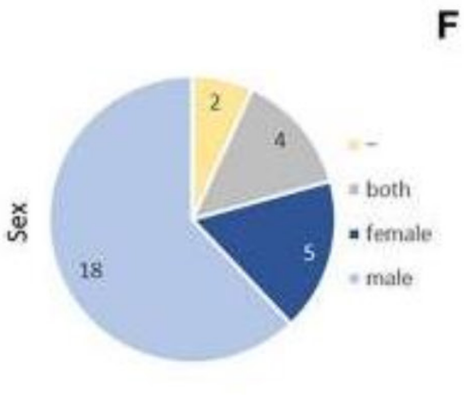
Analgesia and association with anesthetics

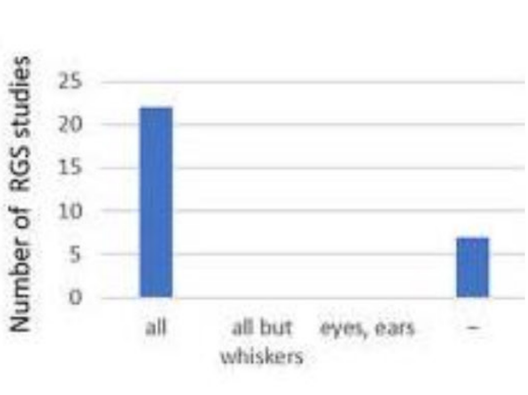




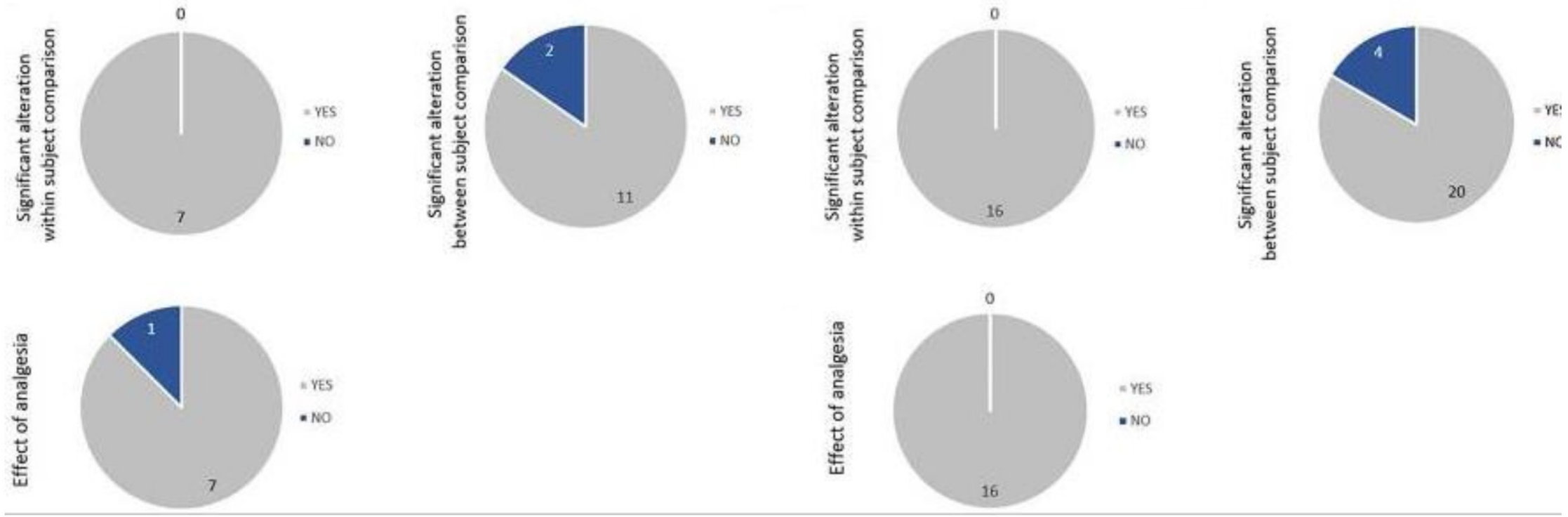








Analgesia and association with anesthetics

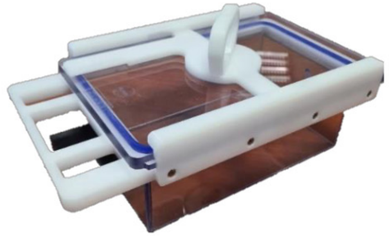


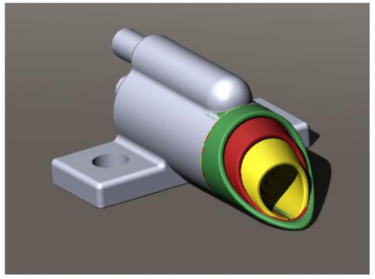
Principles and gaseous anesthesia components

Carrier gas

Vaporizer

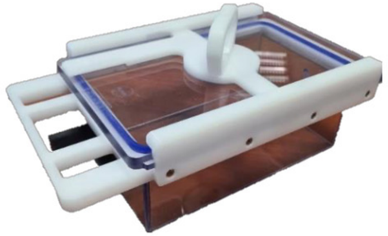
Interface

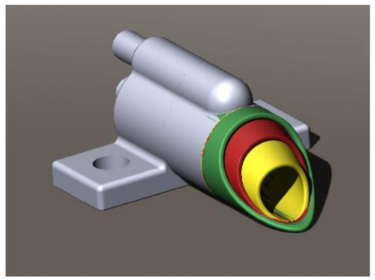




Principles and gaseous anesthesia components

Interface





Expired gas from animal

Principles and gaseous anesthesia components

The carrier gas choice: Air or O2

- Use of an air compressor and/or oxygen concentrator if no presence of an gas outlet
- Possibility to mix the compressed air and the O2
- Oxygen allows for a faster recovery, and prevents hypoxia during long surgeries
- Oxygen can also have negative side effects and have to be carefully administred

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Pages 289–297

Effects of Oxygen Supplementation on Injectable and Inhalant Anesthesia in C57BL/6 Mice

Caroline E Blevins,[1,2] Natalie A Celeste,[3] and James O Marx[1,2,*]

Review > Curr Opin Anaesthesiol. 2012 Jun;25(3):363-70. doi: 10.1097/ACO.0b013e328352b402.

Rational use of oxygen in medical disease and anesthesia

Christian S Meyhoff [1], Anne K Staehr, Lars S Rasmussen

Affiliations + expand

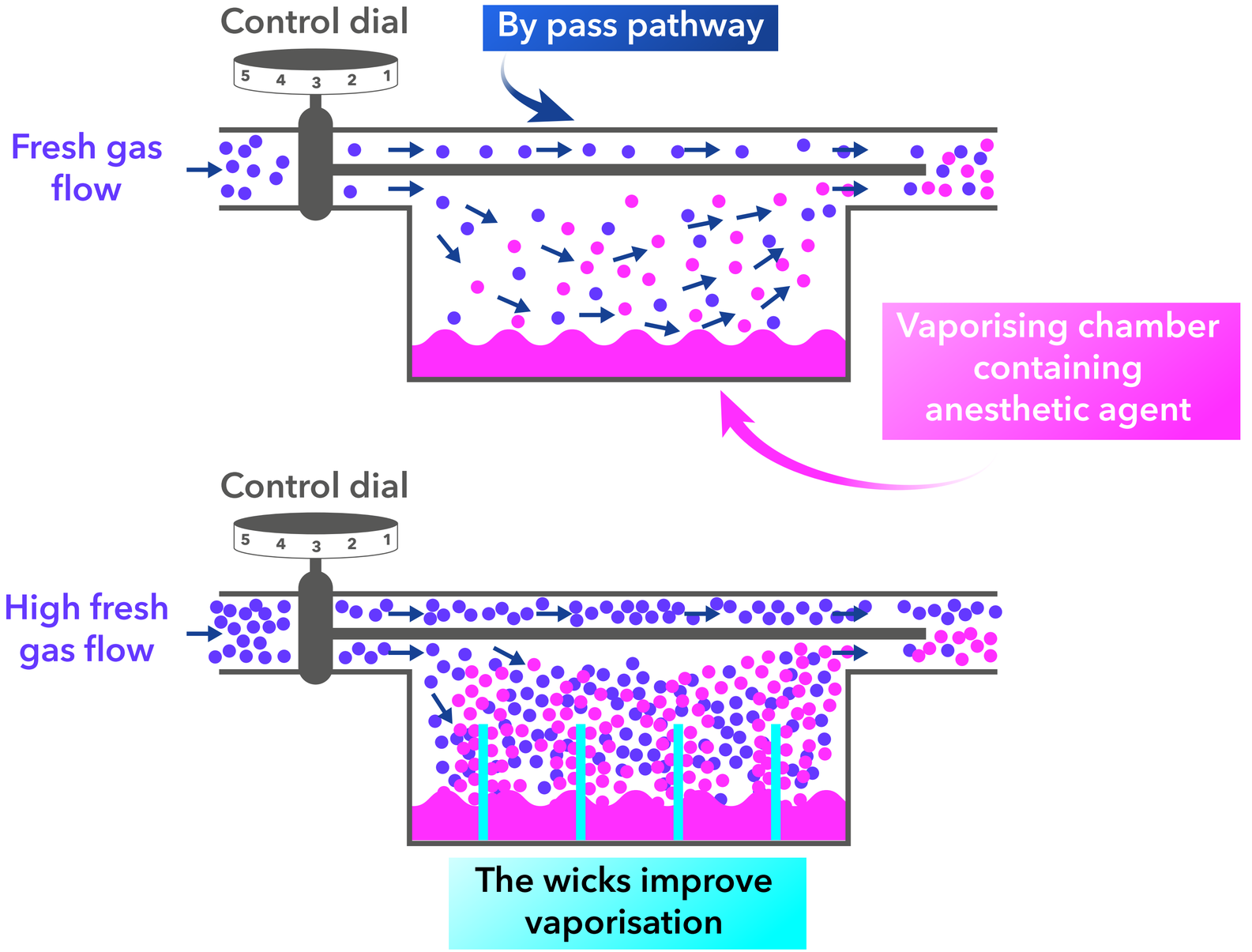
PMID: 22450697 DOI: 10.1097/ACO.0b013e328352b402

Principles and gaseous anesthesia components

The vaporizer: How does it work?

- Vaporizer specific for one gas type: isoflurane, sevoflurane etc...
- Temperature and pressure defined in the chamber
- Concentration range from 0 to 5%
- Filling the vaporizer on the OFF position and with gas source OFF

Principles and gaseous anesthesia components

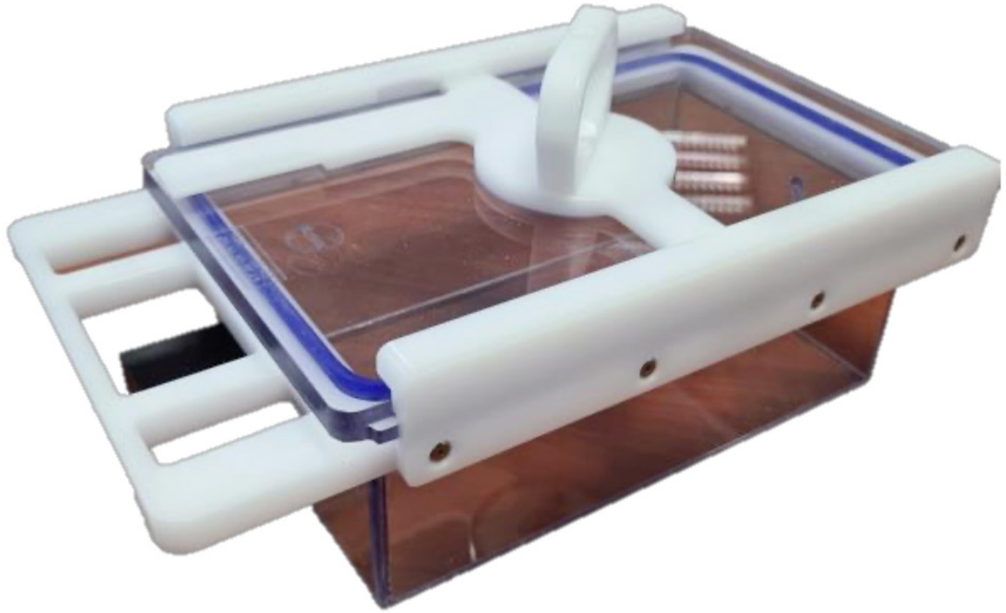


Principles and gaseous anesthesia components

First anesthesia step: Induction in a box

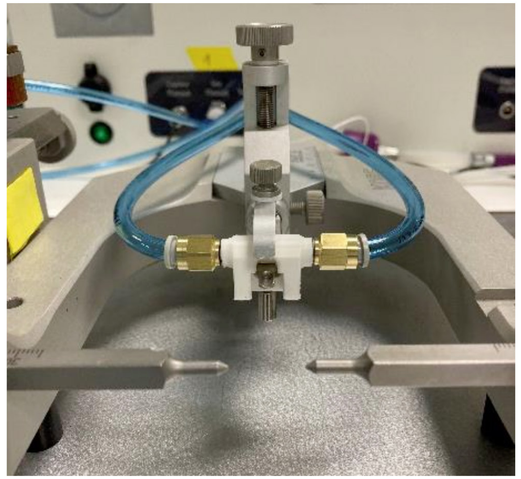
- 2L/min flow (has to be adapted depending on the box volume)
- Possibility to mix the compressed air and the O2
- Optimal induction in 2 min to avoid the stres longer induction, without increasing the flow can lead to the anesthesia stage 4

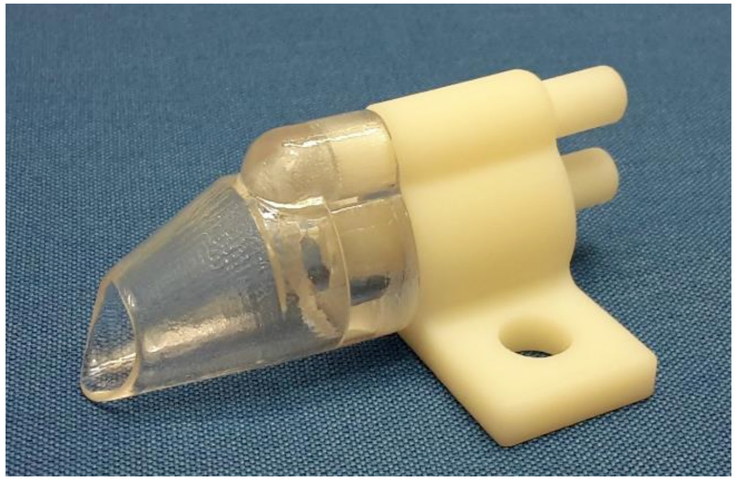
- ✔ Observe for loss of righting reflex
- ✔ Leave animal in chamber for one additional



Principles and gaseous anesthesia components

Second anesthesia step: Maintenance with a mask





- A mask for each application
- Maintain concentration between 1 and 3%
- Animals shoud not respond to noxious stimuli: toe pinch
- Respiration should be regular
- Flow has to be adapted to the animal

Effects of reduction of carrier gas flow rate on sevoflurane and isoflurane consumption and costs

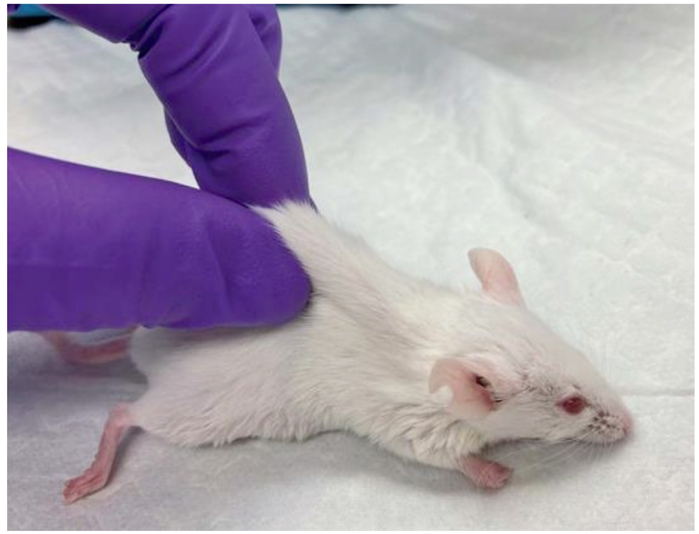
Satoru Tanaka, Hideaki Tsuchida, Hajime Sonoda & Akiyoshi Namiki

Results

Halving the carrier gas flow rate reduced the consumption of sevoflurane by 41.8% and that of isoflurane by 52.6%. It also reduced the total cost by 44.3% for sevoflurane and 49.2% for isoflurane.

Pre-intra and post-operative assessments

Parameters to evaluate	Normal findings
General appearence	Active, smooth fur coat
Respiratory function	Breats not noticeable
Skin coloration	Pink
Hydration	Normal skin turgor
Body condition scoring	2.5 - 3



BC 1

Mouse is emaciated.
- *Skeletal structure extremely prominent; little or no flesh cover.*
- *Vertebrae distinctly segmented.*

BC 2

Mouse is underconditioned.
- *Segmentation of vertebral column evident.*
- *Dorsal pelvic bones are readily palpable.*

BC 3

Mouse is well-conditioned.
- *Vertebrae an dorsal pelvis not prominent; palpable with slight pressure.*

BC 4

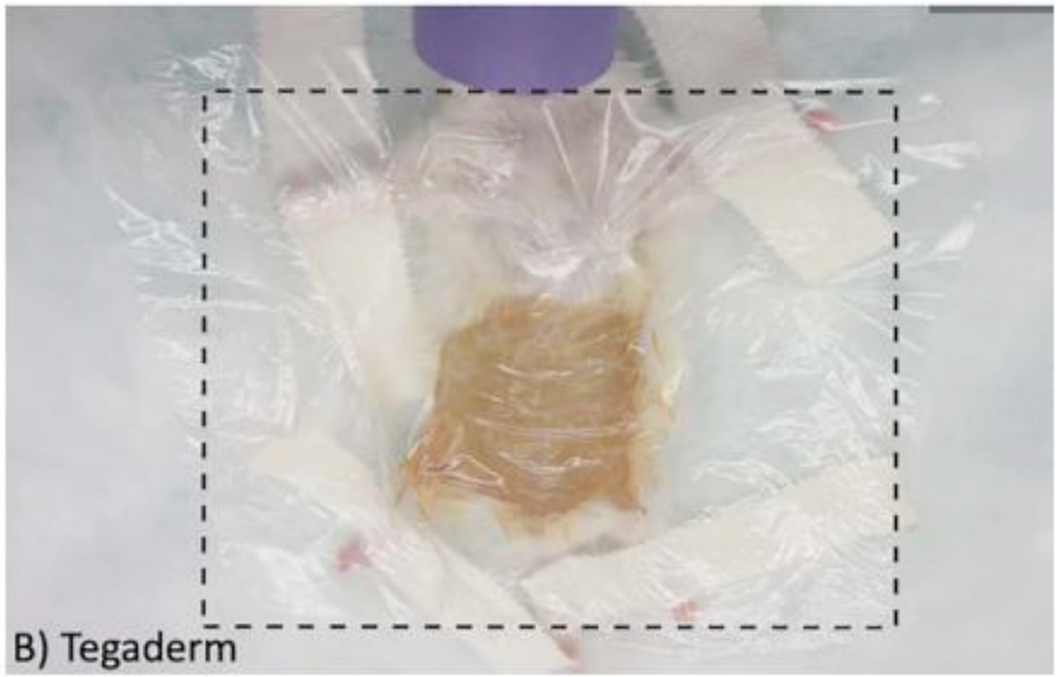
Mouse is overconditioned.
- *Spine is a continuous column.*
- *Vertebrae palpable only with firm pressure.*

BC 5

Mouse is obese.
- *Mouse is smooth and bulky.*
- *Bone structure disappears under flesh and subcutaneous fat.*

Pre-intra and post-operative assessments

- Shaving, aseptic preparation with betadine and alcohol
- Eye lubricant application



- Use of a translucent surgical drape will facilitate monitoring of respiratory function
- Can provide insulation to minimize heat loss

Pre-intra and post-operative assessments

PLoS One. 2020 Mar 3;15(3):e0219722. doi: 10.1371/journal.pone.0219722. eCollection 2020.

Pre-warming before general anesthesia with isoflurane delays the onset of hypothermia in rats

Maxime Rufiange [1 2], Vivian S Y Leung [1 2], Keith Simpson [3], Daniel S J Pang [1 2]

- Prevention of the central hypothermia mandatory
- Regulation of body temperature from 30 to 45 ° C

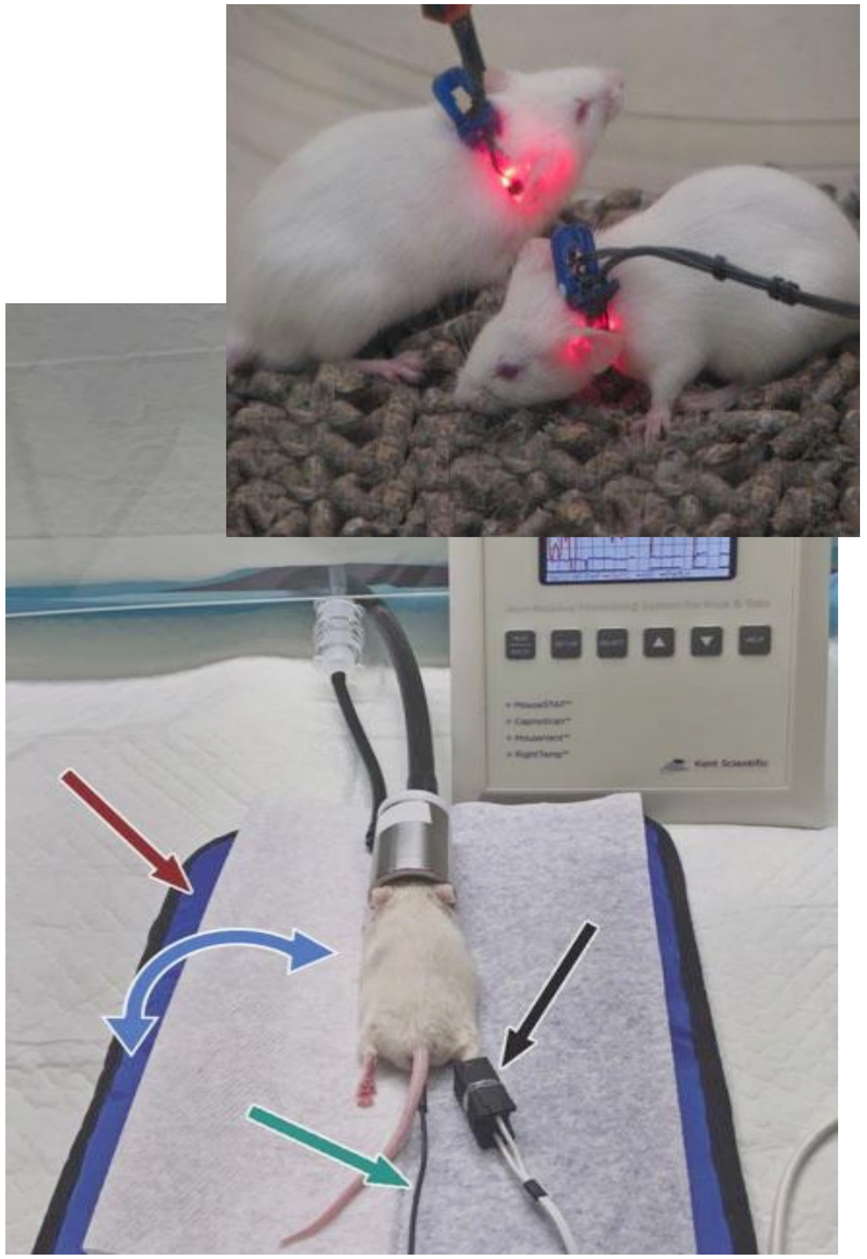
Med Hypotheses. 2019 Dec;133:109387. doi: 10.1016/j.mehy.2019.109387. Epub 2019 Aug 30.

Hypothermia-rewarming: A Double-edged sword?

Yi Hou [1], Yuanyuan Qiao [2], Ming Xiong [3], Dajin Zhang [4], Wei Rao [5], Chenghe Shi [6]

Pre-intra and post-operative assessments

- Body temperature
- Pulse-oximetry
  - BodSPO2 values <95% indicates the onset of mild hypoxia and a reduction to 90% requires immediate actiony temperature
  - If the anesthetic plane is too light, heart rate may increase and if the anesthetic plane is too deep, heart rate drops and can be erratic
- Blood pressure
- Capnography
  - High ETCO2 or hypercapnia indicates hypoventilation, which may be caused by deep anesthetic plane
  - Low ETCO2 or hypocapnia indicates hyperventilation, which may be from reduced cardiac output, blood pressure, decrease in pulmonary perfusion



Gaseous anesthesia parameters

Espèces	Poids (kg)	Fréquence ventilatoire (c/min)	Volume courant (ml)	Fréquence cardiaque (b/min)	Volume sanguin (ml/kg)	Température centrale (°C)
Souris	0.03	180	0.15	550-600	75	37.4
Hamster	0.08	80	0.8	350	72	37.4
Gerbille	0.09	90	0.9	260-600	75	39
Rat	0.2	90	1.6	350	58	38
Cobaye	0.5	120	205	155	75	38
Chat	3	26	30	150	85	38.6
Lapin	3	50	20	220	70	38
Primate	10	35	50	150	75	39
Chien	15	25	150	100	80	38.3
Porc	20	18	420	80	70	39
Mouton	45	20	300	75	60	39.1
Chèvre	50	20	325	80	70	39.4
Porc	200	12	3800	9	65	39

Gaseous anesthesia parameters

Factors affecting anesthesia

- Consider these factors during the anesthesia planning and implementation to ensure optimal research results and preserve research reproducibility
- The consideration of these factors also allows the modern mouse researcher to move towards a more tailored anesthesia, similar to current human anesthesia trends

Strain	Sex	Age	Skill	Duration
MAC and convulsivity threshold differed among strains	Physiological differences may change the anesthetic potency	MAC decreases with age		

Gaseous anesthesia parameters

Strain

- Differences in the genetic basis of anesthetic action in mice
- Consistent with results from studies in drosophila and Caenorhabditis elegans
- Indicate several genetic influences on anesthetic action

Strain	Isoflurane
Inbred mice	
129/J	1.31 ± 0.13 (24)
129/SvJ	1.40 ± 0.12 (16)
129/Olahsd	1.37 ± 0.16 (16)
C57BL6/J	1.30 ± 0.11 (24)
C57BL6/Nhsd	1.33 ± 0.08 (24)
DBA/2J	1.60 ± 0.20 (13)
Cast/Ei	1.43 ± 0.31 (7)
Spret/Ei	1.77 ± 0.17 (6)
Hybrid mice	
B6129F2/J	1.33 ± 0.16 (24)
B6129F2/J (Tail tip clipped)	1.67 ± 0.14 (6)
Outbred mice	
CD-1	1.34 ± 0.16 (23)

Gaseous anesthesia parameters

Sex

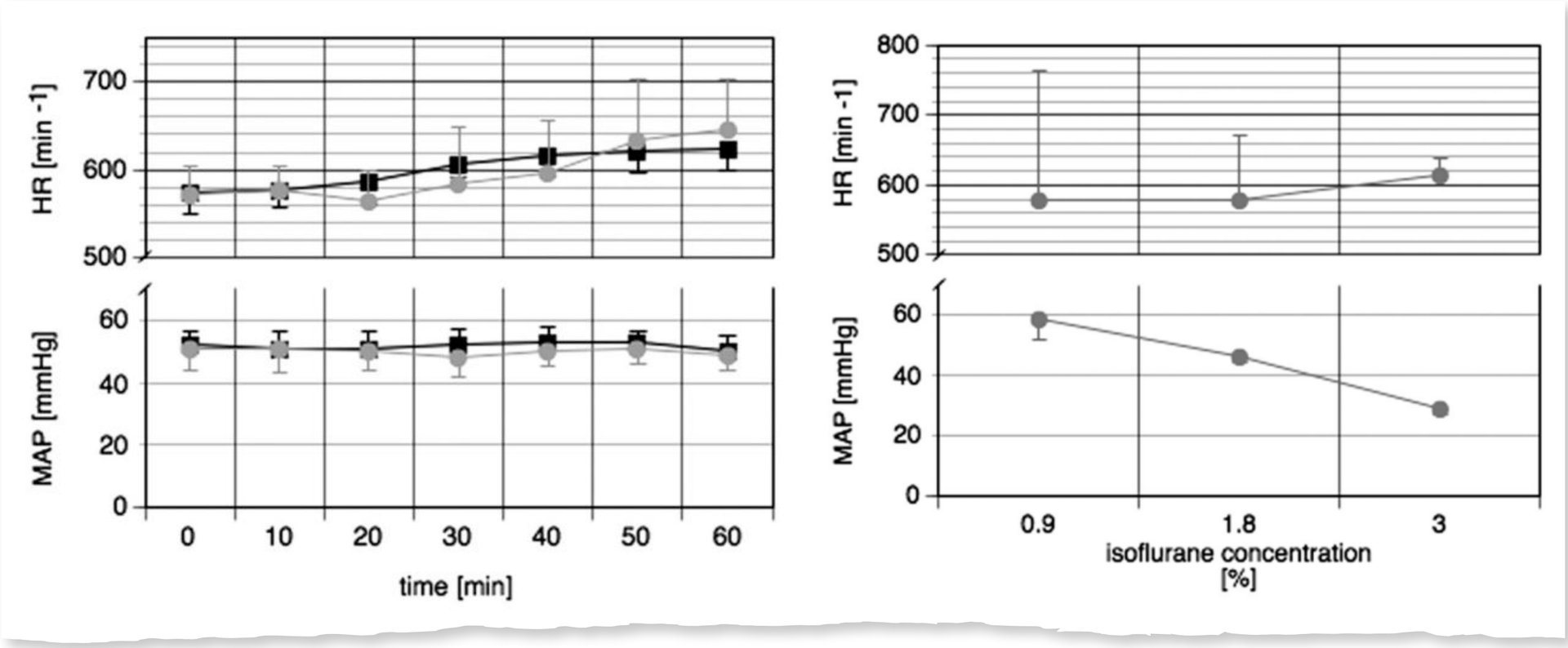
- 79% of animal studies published in Pain over the preceding 10 years included male subjects only, 8% of studies on females only, and another 4% explicitly designed to test for sex differences
- On average, blood pressure, height and weight differ by sex and these differences may affect response to a pain stimulus, as well as responses to pain treatment
- Difference in body fat percentage (adult males > adult females) can affect potency and/or duration of some anesthetic and analgesic agents

Age

- MAC for volatile inhalant anesthesia decreases with age in humans and animals, including mice
- Minimum alveolar concentration (MAC) was 2.3% in 10-day-old mice

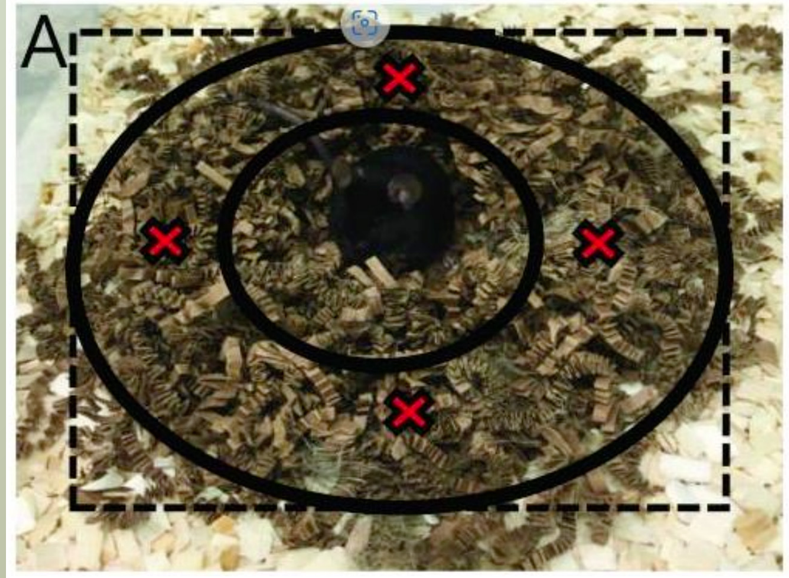
Gaseous anesthesia parameters

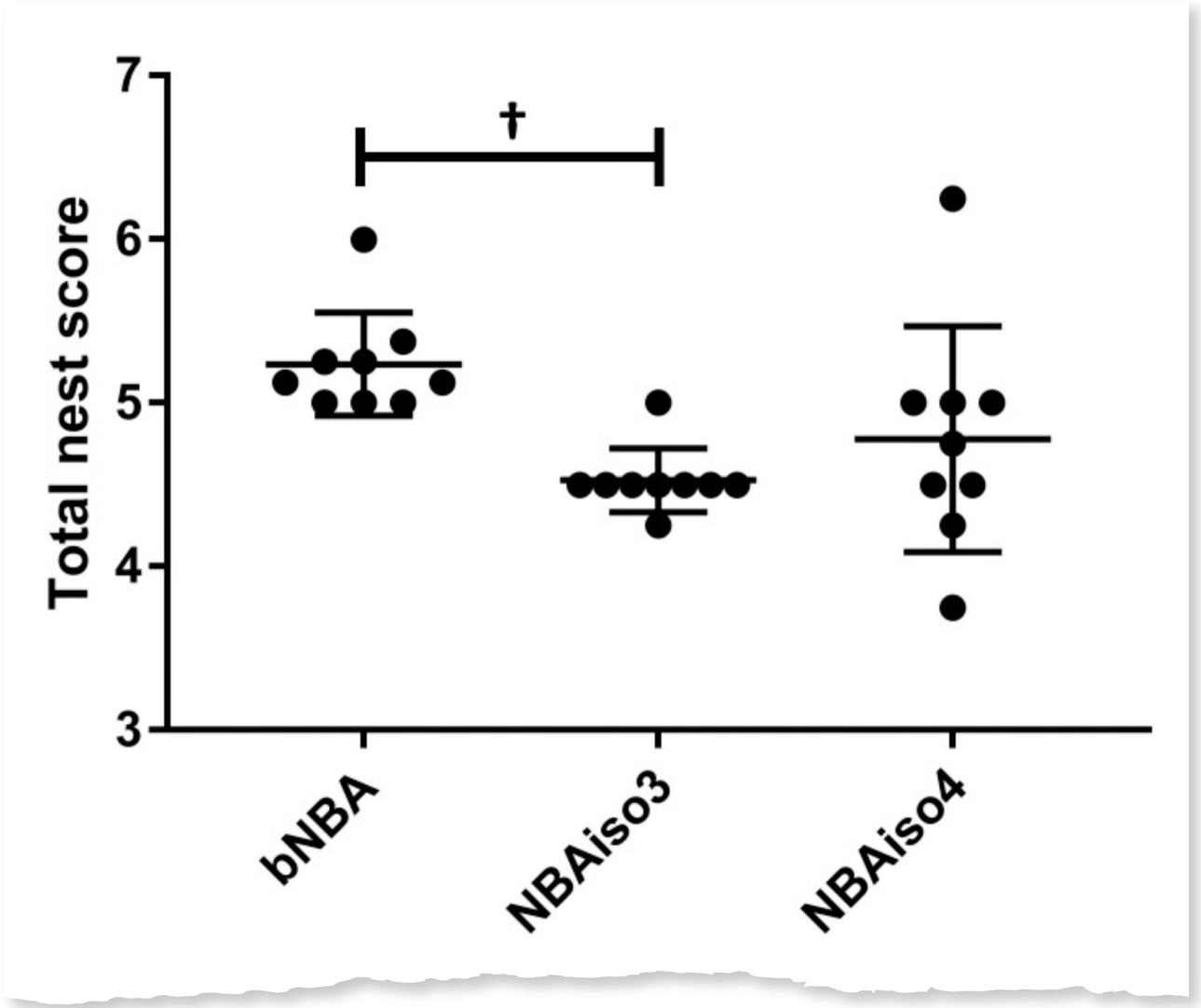
Duration and operator skill



In cardiology research, prolonged anesthesia (isoflurane or sevoflurane) affects blood vessel contractility for several days after the anesthetic event

Gaseous anesthesia parameters

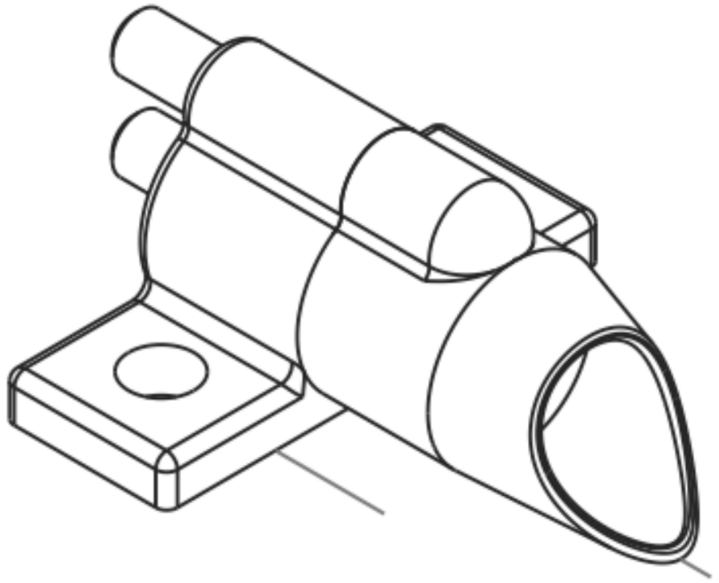




Gaseous anesthesia parameters

Anesthesia in neonates

- Propensity to develop hypothermia and hypoglycemia
- Increased blood–brain barrier permeability
- Higher body-water content
- Less mature hepatic system
- Lower albumin concentrations
- Less mature pulmonary system

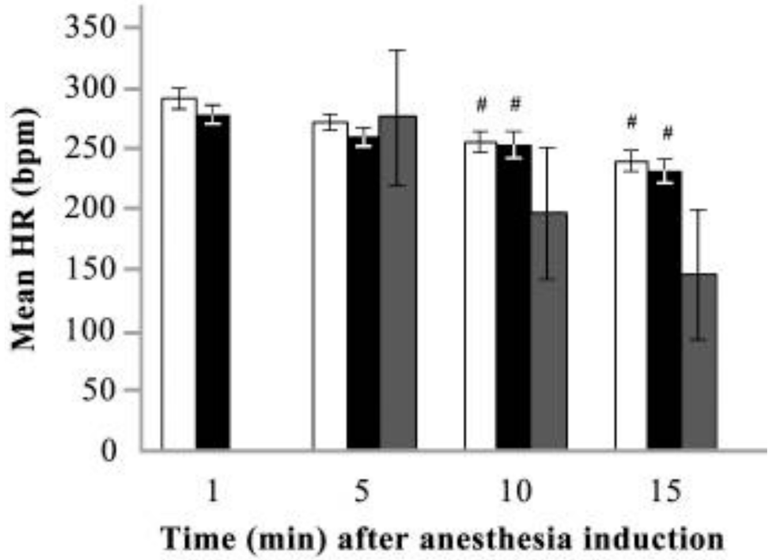


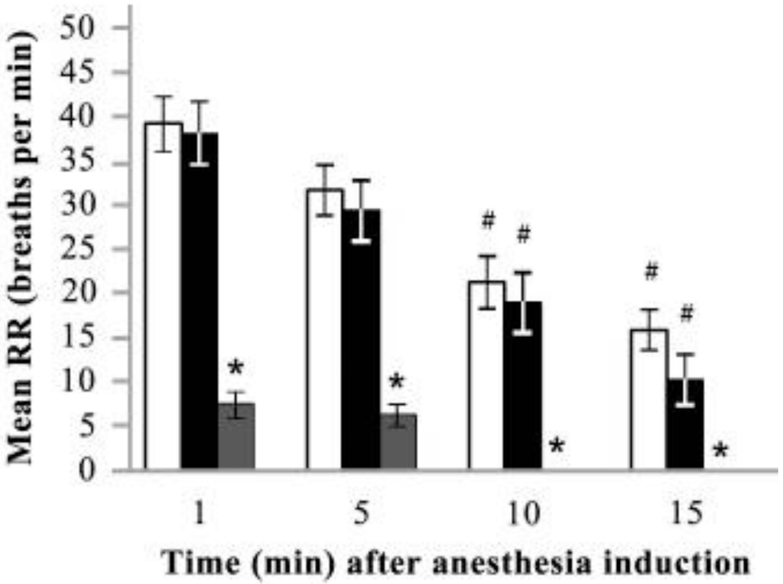
Gaseous anesthesia parameters

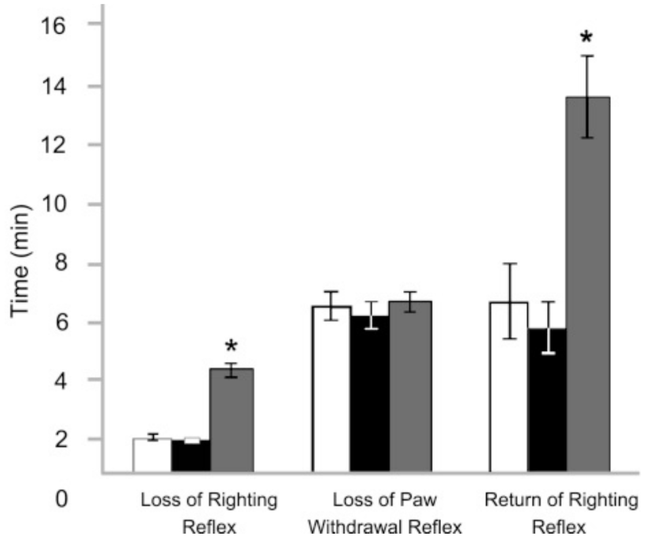
- Up to 7 days (poikilothermic for up to 7 days) and no longer than 30 minutes
- Small body mass = surface cooling quickly decreases their body temperature
- Placed on top of a latex sleeve in an ice bath and held in position
- Bradycardia, hypoventilation or apnea and hypoxemia are all seen in the first 5–15 minutes of neonatal hypothermia anesthesia
- Provide gradual rewarming, because rapid warming, such as with a heating lamp, can lead to tissue damage

Gaseous anesthesia parameters

- Induction chamber at 2 L/min of 100% O2 containing either 5% isoflurane or 8% sevoflurane
- Mask with 0.5L/min and 3% isoflurane or 5% sevoflurane
- Shorter recovery time



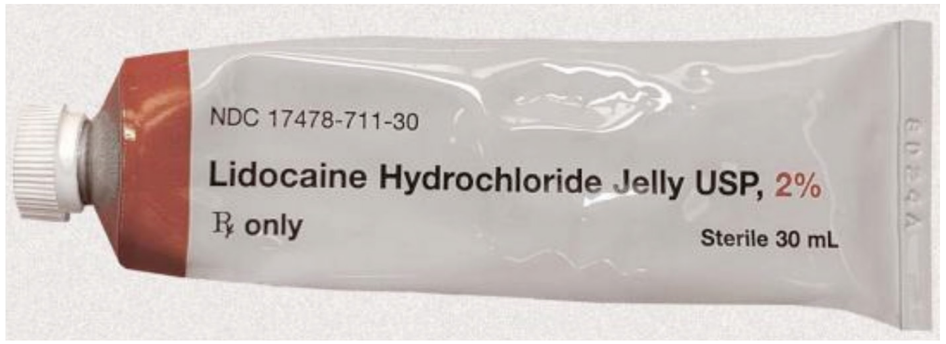


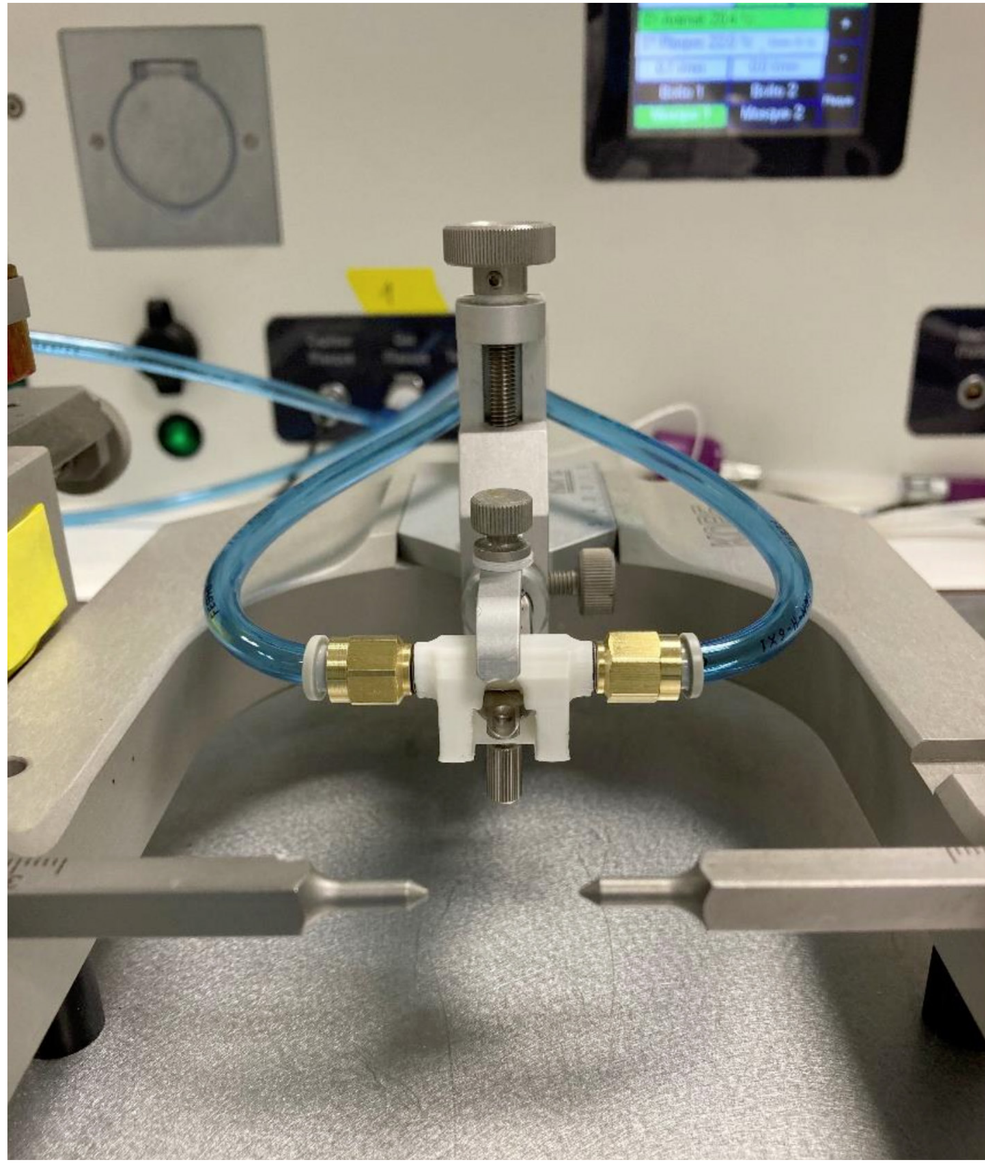


Gaseous anesthesia parameters

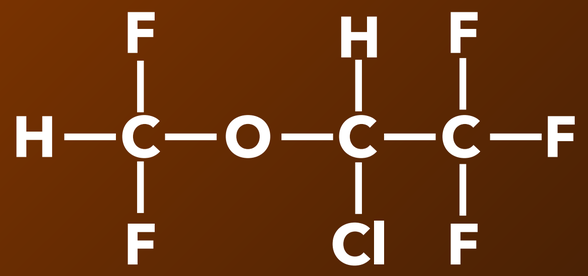
Anesthesia in stereotaxic procedures

- 3D printed masks to improve head placement
- Absent paw withdrawal reflex before placing ear bars
- Coating the ear bars tips with lidocaine
- Removing the ear bars at the end can deepen the anesthesia state





Anesthetic exposure and safety



Isoflurane, 1-chloro-2,2,2-trifluoroethyl difluoromethyl, Forane®, Aerrane®, Isorrane®, Isovet®

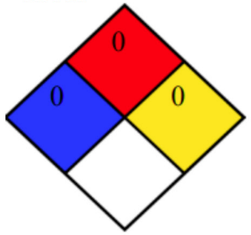
WHMIS 1988

D2B: Poisonous and infectious material: other toxic effects
Chronic toxicity; Specific target organ toxicity - single exposure

WHMIS 2015

Eye irritation (Category 2B)
Specific target organ toxicity - single exposure (Category 3): central nervous system
Specific target organ toxicity - repeated exposure, Inhalation (Category 2): cardio- vascular system and central nervous system

NFPA



Flammability: Non-Flammable
Health hazard: Normal material
Instability/Reactivity: Stable

Anesthetic exposure and safety

SIGMA-ALDRICH sigma-aldrich.com

SAFETY DATA SHEET

according to Regulation (EC) No. 1907/2006
Version 5.4 Revision Date 02.06.2015
Print Date 25.04.2017
GENERIC EU MSDS - NO COUNTRY SPECIFIC DATA - NO OEL DATA

Skin protection
Handle with gloves. Gloves must be inspected prior to use. Use proper glove removal technique (without touching glove's outer surface) to avoid skin contact with this product. Dispose of contaminated gloves after use in accordance with applicable laws and good laboratory practices. Wash and dry hands.

The selected protective gloves have to satisfy the specifications of EU Directive 89/686/EEC and the standard EN 374 derived from it.

Body Protection
Complete suit protecting against chemicals, The type of protective equipment must be selected according to the concentration and amount of the dangerous substance at the specific workplace.

Respiratory protection
Where risk assessment shows air-purifying respirators are appropriate use a full-face respirator with multi-purpose combination (US) or type ABEK (EN 14387) respirator cartridges as a backup to engineering controls. If the respirator is the sole means of protection, use a full-face supplied air respirator. Use respirators and components tested and approved under appropriate government standards such as NIOSH (US) or CEN (EU).

Anesthetic exposure and safety

Early Postnatal Exposure to Isoflurane Disrupts Oligodendrocyte Development and Myelin Formation in the Mouse Hippocampus.

Qun Li, Ph.D., Reilley P. Mathena, B.S., Jing Xu, M.D., O'Rukevwe N. Eregha, B.A., Jieqiong Wen, B.S., and Cyrus D. Mintz, M.D., Ph.D.

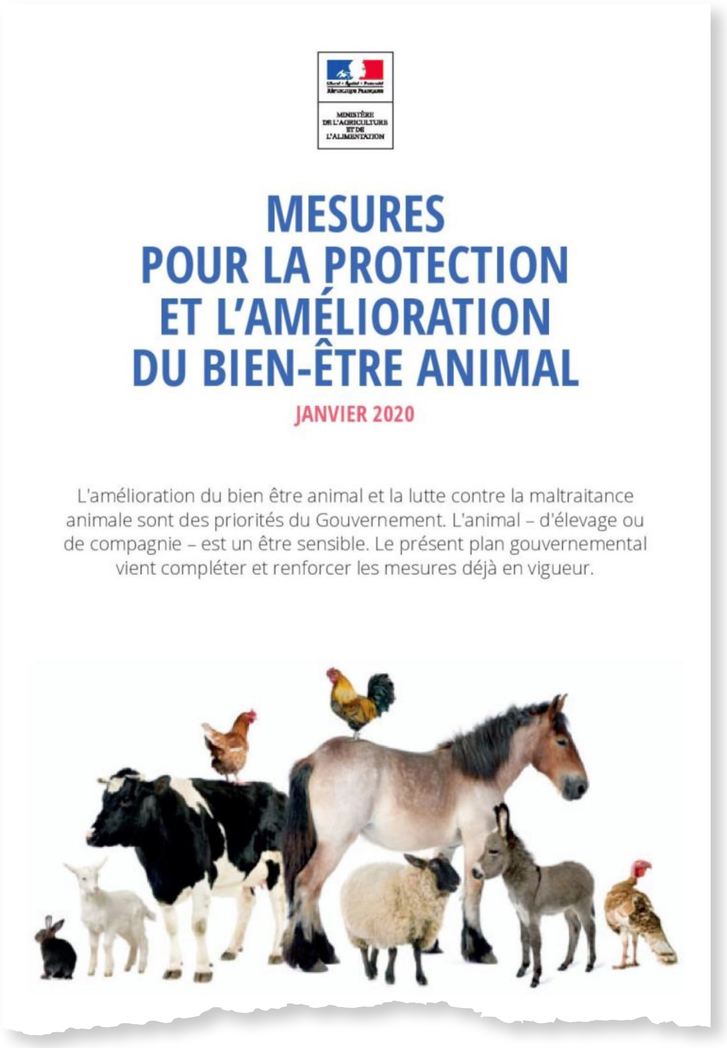
Conclusions:

Early postnatal exposure to isoflurane in mice causes lasting disruptions of oligodendrocyte development in the hippocampus via actions on the mTOR pathway.

Early postnatal exposure to isoflurane causes cognitive deficits and disrupts development of newborn hippocampal neurons via activation of the mTOR pathway

Eunchai Kang, Investigation, Methodology, Supervision, Writing – original draft,[#1,2] Danye Jiang, Investigation, Writing – original draft,[#3] Yun Kyoung Ryu, Conceptualization, Investigation, Methodology, Supervision,[#3] Sanghee Lim, Investigation,[3] Minhye Kwak, Investigation,[3] Christy D. Gray, Investigation, Writing – original draft,[3] Michael Xu, Investigation, Writing – review & editing,[3] Jun H. Choi, Investigation,[1,¶] Sue Junn, Investigation,[1] Jieun Kim, Investigation,[1] Jing Xu, Writing – review & editing,[3] Michele Schaefer, Writing – original draft, Writing – review & editing,[3] Roger A. Johns, Conceptualization, Resources, Supervision, Writing – review & editing,[3] Hongjun Song, Conceptualization, Methodology, Resources, Supervision, Writing – review & editing,[1,2,4] Guo-Li Ming, Conceptualization, Methodology, Resources,[1,2,4] and C. David Mintz, Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Visualization, Writing – original draft, Writing – review & editing[3,*]

Anesthetic exposure and safety



MINISTÈRE DE L'AGRICULTURE ET DE L'ALIMENTATION

MESURES POUR LA PROTECTION ET L'AMÉLIORATION DU BIEN-ÊTRE ANIMAL

JANVIER 2020

L'amélioration du bien être animal et la lutte contre la maltraitance animale sont des priorités du Gouvernement. L'animal – d'élevage ou de compagnie – est un être sensible. Le présent plan gouvernemental vient compléter et renforcer les mesures déjà en vigueur.

- la perte de l'équilibre, et des réflexes posturaux = stade d'anesthésie débutante

- le nystagmus (inconstant) = passage à l'anesthésie chirurgicale (ou au contraire début du réveil)

- l'insensibilité au pincement des oreilles, de la queue et des espaces interdigités = anesthésie chirurgicale (début)

- l'abolition du réflexe d'extension du membre au pincement de la corde du jarret (lapin) ou à la percussion du ligament patellaire chez les grands animaux (réflexe rotulien) = anesthésie chirurgicale correcte

- la disparition du réflexe oculo-palpébral. Attention, il est difficile à tester et peu fiable chez les petites espèces - la persistance du réflexe cornéen = stade toxique - la surveillance de la fréquence de la respiration (danger si chute de 40% = stade toxique; si accélération = réveil ou excès de CO_2 veineux si anesthésie volatile)

- la couleur des muqueuses (blanches ou danger de syncope et d'apnée)

- la température centrale (risque d'hypothermie)

No mandatory guidelines, only issued recommandations

Anesthetic exposure and safety

	origine	Valeur moyenne pondérée	Valeur au cours d'une courte exposition
France	Recommandé par la Comission Française d'Anesthésiologie et transcrite par une circulaire du Ministère de la Santé DGS/3A/667 bis du 10 octobre 1985	2 ppm à proximité du patient pendant la phase d'entretien de l'anesthésie	–
Allemagne	Limite règlementaire depuis 1994	10 ppm	–
Angleterre	Seuil limite depuis 1996 établi par COSHH (The Control of Substances Hazardous to Health Regulation)	50 ppm	–
Danemark	Valeur limite depuis 1988	2 ppm	–
Finlande		10 ppm	–
Norvège	Valeur limite depuis 1991	2 ppm	–
Polande	The Expert Group for Chemical Hazards	4 ppm	–
Quebec	Valeur limite depuis 1995	75 ppm	–
Suède	Valeur limite depuis 1990	10 ppm	–
Suisse	Valeur limite depuis 1997	10 ppm sur 8 heures	20 ppm sur une durée 4 fois 30 minutes par période de travail
USA	Nationnal Institute of Occupationnal Safety and Health (NIOSH), organisme officiel	2 ppm ou 0,5ppm en présence de N2O pour un prélèvement d'une heure	–
	American Conference of Governmental Industrial Hygiene (ACGIH), association de droit privé	75 ppm	< 3 fois la valeur moyenne et pas plus 30 minutes sur une journée de travail

Circulaire DGS/3A/667 bis du 10 Octobre 1985 relative à la distribution des gaz à usage médical et à la création d'une commission locale de surveillance de cette distribution.

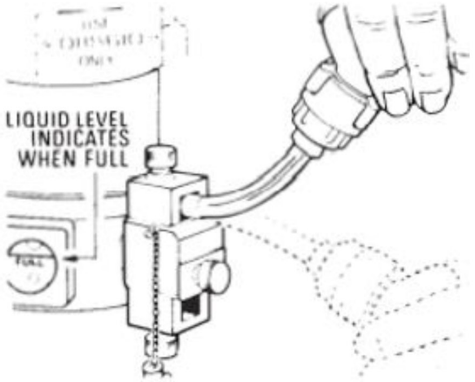
IV – Propositions concernant la pollution par les gaz et vapeur anesthésiques

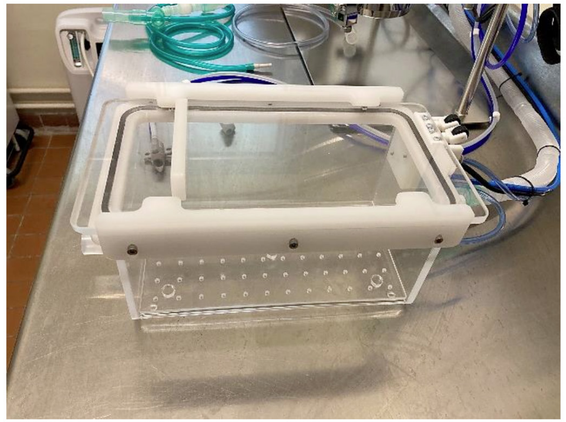
Proposition n° 1 – Les salles où se font les anesthésies (y compris l'induction et le réveil) doivent être équipées de dispositifs assurant l'évacuation des gaz et vapeurs anesthésiques. Ces dispositifs doivent permettre, durant la phase d'entretien de l'anesthésie, d'abaisser à proximité du malade et du personnel les concentrations :

- à moins de 25 ppm pour le protoxyde d'azote ;
- à moins de 2 ppm pour les halogènes.

Proposition n° 2 – La commission locale de surveillance doit s'assurer de la réalisation des mesures prévues ci-dessus, en liaison avec le comité d'hygiène et de sécurité et des conditions de travail (CHSCT) de l'établissement et conformément aux dispositions de l'article R. 232-12 du code du travail (Assainissement, gaz toxiques).

Anesthetic exposure and safety





Anesthetic exposure and safety

Expired gas from animal

- Active charcoal filters are used for the isoflurane adsorption
- Has to be replaced once saturated, and discard in the dasri bin
- HEPA filters can be used to ensure no contamination by any biological agent

Merci de votre attention

TEM SEGA
One touch device

Équipements pour
la recherche scientifique et
préclinique

AFSTAL 2023
Du 7 au 9 juin 2023 - BORDEAUX
47e Colloque Afstal