



References on the Administration of Metals  
Using ALZET® Osmotic Pumps

Arsenate

**P1078:** D. P. Hanlon, *et al.* The concentration and chemical status of arsenic in the early placentas of arsenate-dosed hamsters. *Environmental Research* 1987;42(546-552

**Agents:** Arsenate, sodium; Radio-isotopes **Vehicle:** Arsenic-74 tracer; Water; Radio-isotopes; **Route:** Not Stated; **Species:** Hamster (pregnant); **Pump:** 2001; **Duration:** 8 days;

**ALZET Comments:** Functionality of mp verified by radioassay; teratology

**P0899:** D. P. Hanlon, *et al.* Concentration and chemical status of arsenic in the blood of pregnant hamsters during critical embryogenesis. *Environmental Research* 1986;40(372-379

**Agents:** Arsenate, sodium **Vehicle:** Not Stated; **Route:** SC; **Species:** Hamster; **Pump:** 2001; **Duration:** 24, 48, 72, 168 hours;

**ALZET Comments:** Teratology; dose-response; functionality of mp verified by radio assay

**P0673:** V. H. Ferm, *et al.* Constant rate exposure of pregnant hamsters to arsenate during early gestation. *Environmental Research* 1985;37(2):425-432

**Agents:** Arsenate, sodium **Vehicle:** Water; **Route:** SC; **Species:** Hamster (pregnant); **Pump:** 2001; **Duration:** 6-9 days;

**ALZET Comments:** Teratogenicity; pumps primed in saline 4 hr prior to implant; dose-response data, 4 doses tested;

Cadmium

**P9987:** H. C. Pedersen, *et al.* Behavioural effects of cadmium (Cd) in free-living willow ptarmigan (*Lagopus lagopus*). *EUROPEAN JOURNAL OF WILDLIFE RESEARCH* 2010;56(2):141-150

**Agents:** Cadmium chloride **Vehicle:** Not Stated; **Route:** SC; **Species:** Bird (hen); **Pump:** 2002; **Duration:** 23 days;

**ALZET Comments:** Controls received mp w/ physiological saline; pumps replaced after 13 days; animal info (willow, ptarmigan, adult, juvenile)

**P6028:** M. Piasek, *et al.* Low iron diet and parenteral cadmium exposure in pregnant rats: the effects on trace elements and fetal viability. *Biomedicine & Pharmacotherapy* 2004;17(1):1-14

**Agents:** Cadmium chloride **Vehicle:** Saline; **Route:** SC; **Species:** Rat (pregnant); **Pump:** 2ML4; **Duration:** 28 days;

**ALZET Comments:** Dose-reponse (p. 7, table 2); comparison of SC injections vs. SC mp; teratology

**P5804:** M. Kondoh, *et al.* Property of metallothionein as a Zn pool differs depending on the induced condition of metallothionein. *TOXICOLOGY LETTERS* 2003;142(1-2):11-18

**Agents:** Cadmium acetate **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Pump:** Not Stated; **Duration:** 14 days;

**ALZET Comments:** Controls received mp w/ vehicle; no stress (see pg. 12) "None of the animals displayed any evidence of infection or other adverse effects from the procedure."; toxicology

**P6661:** M. Piasek, *et al.* Assessment of steroid disruption using cultures of whole ovary and/or placenta in rat and in human placental tissue. *International Archives of Occupational and Environmental Health* 2002;75(S36-S44

**Agents:** Cadmium chloride **Vehicle:** Not Stated; **Route:** SC; **Species:** Rat (pregnant); **Pump:** 2ML2; **Duration:** 19 days;

**ALZET Comments:** Functionality of mp verified by placental cadmium levels; dose-response (fig. 5); teratology

**P4430:** Z. A. Shaikh, *et al.* Dependence of cadmium-metallothionein nephrotoxicity on glutathione. *Journal of Toxicology and Environmental Health* 1999;56(211-222

**Agents:** Cadmium metallothionein **Vehicle:** Saline; **Route:** Not Stated; **Species:** Rat; **Pump:** 2001D; **Duration:** 24 hours;

**ALZET Comments:** Control received mp w/vehicle; comparison of bolus injections vs. mp; toxicology; dependence

**P3562:** S. L. Curtis, *et al.* Subacute exposure to cadmium chloride induces HSP-72 in rat liver. *Res. Commun. Mol. Path. Pharmacol* 1996;94(2):221-224

**Agents:** Cadmium chloride **Vehicle:** Not Stated; **Route:** SC; **Species:** Rat; **Pump:** 2001; **Duration:** 14 days;

**ALZET Comments:** controls received mp w/ dl H<sub>2</sub>O, toxicology



**P2792:** M. P. Mahalik, *et al.* Teratogenic effects and distribution of cadmium (Cd<sup>2+</sup>) administered via osmotic minipumps to gravid CF-1 mice. *Toxicol. Lett* 1995;76(195-202)

**Agents:** Cadmium **Vehicle:** Saline, sterile; **Route:** SC; **Species:** Mice (pregnant); **Pump:** Not Stated; **Duration:** 14 days;  
**ALZET Comments:** Controls received no treatment or mp w/saline; functionality of mp verified by testing blood levels of cadmium; no stress (see pg. 196); teratology; investigators state that disinfectant is not necessary for sc implantation; there is no infection or other complication

**P3026:** P. Vestergaard, *et al.* The nephrotoxicity of intravenously administered cadmium-metallothionein: effect of dose, mode of administration, and preexisting renal cadmium burden. *Toxicol. Appl. Pharmacol* 1994;126(240-247)

**Agents:** Cadmium metallothionein **Vehicle:** Radio-isotopes; Potassium phosphate buffer; Mercaptoethanol, 2-; **Route:** IV (jugular); **Species:** Rat; **Pump:** Not Stated; **Duration:** 24 hours;  
**ALZET Comments:** dose response; comparison of sc injections vs. mp; toxicology; Cd-MT was well tolerated if given via infusion, but nephrotoxic if given as a bolus injection

**P0966:** I. S. Jamall, *et al.* Effects of cadmium and dietary selenium on cytoplasmic and mitochondrial antioxidant defense systems in the heart of rats fed high dietary copper. *Toxicol. Appl. Pharmacol* 1987;87(102-110)

**Agents:** Cadmium chloride **Vehicle:** Not Stated; **Route:** SC; **Species:** Rat; **Pump:** 2002; **Duration:** 2 weeks;  
**ALZET Comments:** comparison of cadmium in diet vs. mp infusion

**P1172:** G. DuVal, *et al.* Tissue accumulation of cadmium as a function of blood concentration. *Biological Trace Element Research* 1986;9(2):101-111

**Agents:** Cadmium chloride **Vehicle:** Not Stated; **Route:** SC; **Species:** Rabbit; **Pump:** 2ML4; **Duration:** 28 days;  
**ALZET Comments:** controls received sham operation; dose-response; stress/adverse reaction (fibrous tissue covering mp)

**P0716:** I. S. Jamall, *et al.* Effects of cadmium on glutathione peroxidase, superoxide dismutase, and lipid peroxidation in the rat heart: a possible mechanism of cadmium cardiotoxicity. *Toxicol. Appl. Pharmacol* 1985;80(1):33-42

**Agents:** Cadmium chloride **Vehicle:** Water; **Route:** SC; **Species:** Rat; **Pump:** 2001; **Duration:** Not Stated;  
**ALZET Comments:** Controls received mp w/ deionized water; Cd administered in diet and mp infusion; Se eliminated or supplemented in diet

**P0636:** I. S. Jamall, *et al.* The effects of dietary selenium on cadmium binding in rat kidney and liver. *Archives of Pharmacal Research* 1985;56(4):252-255

**Agents:** Cadmium chloride **Vehicle:** Not Stated; **Route:** SC; **Species:** Rat; **Pump:** 2001; **Duration:** Not Stated;  
**ALZET Comments:** Duration of mp use probably 1 week; purpose for mp use not clear, Cd delivered primarily in diet for 7 weeks

**P0136:** D. R. Johnson, *et al.* On the proposed role of metallothionein in the transport of cadmium. *Environmental Research* 1980;21(2):360-365

**Agents:** Cadmium chloride; Cadmium metallothionein; Radio-isotopes **Vehicle:** 109CdCl<sub>2</sub> tracer; 109CdMt tracer; Radio-isotopes; **Route:** SC; **Species:** Rat; **Pump:** Not Stated; **Duration:** 2, 3 days;  
**ALZET Comments:** Comparison of injections in rabbits vs. mp infusion in rats

### Copper

**P8422:** N. Lavoie, *et al.* Extracellular chelation of zinc does not affect hippocampal excitability and seizure-induced cell death in rats. *Journal of Physiology-London* 2007;578(1):275-289

**Agents:** Tricine; EDTA, copper; EDTA, zinc; EDPA; EDTA, calcium **Vehicle:** Saline; resyl violet; **Route:** CSF/CNS; **Species:** Rat; **Pump:** 2001D; **Duration:** 12 hours;  
**ALZET Comments:** Controls received mp w/ vehicle; functionality of mp verified by residual volume; brain tissue distribution; animal info (male, Sprague-Dawley, >35 days old); cresyl violet used to verify injection site



**P3117:** S. Toyokuni, *et al.* Increased 8-hydroxydeoxyguanosine in kidney and liver of rats continuously exposed to copper. *Toxicol. Appl. Pharmacol* 1994;126(91-97)

**Agents:** Copper chloride; Cupric nitrilotriacetate; Nitrilotriacetic acid **Vehicle:** Not Stated; **Route:** SC; **Species:** Rat; **Pump:** 2001; **Duration:** 3,5 days;

**ALZET Comments:** controls received mp with saline or no treatment; toxicology; Cu-NTA is a copper chelate; copper pump implant sites were marked by tissue necrosis and massive neutrophil infiltration; "...a level of copper that proved to be lethal or highly toxic when delivered in a single bolus dose could be continuously administered with mild histological alterations and without any noticeable modification in the behavior of the rats."

**P1994:** J. B. Ferrell, *et al.* Effect of copper loading and depletion on rabbit superoxide dismutase activity. *Trace Elements in Medicine* 1992;9(2):55-58

**Agents:** Copper sulfate **Vehicle:** Saline; **Route:** SC; **Species:** Rabbit; **Pump:** 2ML4; **Duration:** Not Stated;

**ALZET Comments:** no comment posted

**P1620:** M. C. McGahan, *et al.* Clinical signs of acute ocular inflammatory response to endotoxin are not altered by increasing antioxidant potency of intraocular fluids. *Inflammation* 1989;13(4):383-392

**Agents:** Copper sulfate **Vehicle:** Saline; **Route:** SC; **Species:** Rabbit; **Pump:** 2ML4; **Duration:** Not Stated;

**ALZET Comments:** Uveitis model

**P0890:** J. C. Veltman, *et al.* Regulatory effect of copper on rat adrenal cytochrome P-450 and steroid metabolism. *Biochemical Pharmacology* 1986;35(17):2903-2909

**Agents:** Copper sulfate **Vehicle:** Saline; **Route:** SC; **Species:** Rat; **Pump:** Not Stated; **Duration:** 7 days;

**ALZET Comments:** controls received mp w/ saline

**P0817:** C. S. Cook, *et al.* Experimental hypercupremia does not result in increases in copper in lens, iris, or ocular fluids. *Current Eye Research* 1986;5(2):171-173

**Agents:** Copper sulfate **Vehicle:** Not Stated; **Route:** SC; **Species:** Rabbit; **Pump:** 2ML4; **Duration:** 28 days;

**ALZET Comments:** dose-response data; controls received anesthesia but no surgery or mp

### Iron-saturated

**P2580:** H. Kondo, *et al.* Role of iron in oxidative stress in skeletal muscle atrophied by immobilization. *Pflugers Arch* 1992;421(295-297)

**Agents:** Desferrioxamine; Desferrioxamine, iron-saturated **Vehicle:** Water, double-distilled; **Route:** SC; **Species:** Rat; **Pump:** 2ML1; **Duration:** 8 days;

**ALZET Comments:** controls received mp w/ water

### Magnesium

**Q6695:** L. Liu, *et al.* Increased neuronal seizure activity correlates with excessive systemic inflammation in a rat model of severe preeclampsia. *Hypertens Res* 2016;39(10):701-708

**Agents:** Magnesium sulfate **Vehicle:** Not Stated; **Route:** SC; **Species:** Rat; **Pump:** 2ML1; **Duration:** Not Stated;

**ALZET Comments:** Dose (60 mg/kg/day); animal info (10-12 week old female Sprague Dawley rats weighing 210–250 g); Therapeutic indication (preeclampsia);

**Q3760:** A. C. Johnson, *et al.* Magnesium Sulfate Treatment Reverses Seizure Susceptibility and Decreases Neuroinflammation in a Rat Model of Severe Preeclampsia. *PLoS One* 2014;9(U1482-U1492)

**Agents:** Magnesium sulfate **Vehicle:** Not Stated; **Route:** SC; **Species:** Rat (pregnant); **Pump:** Not Stated; **Duration:** Not Stated;

**ALZET Comments:** Animal info (Sprague Dawley, 14-16 wks old); multiple pumps (3) used; 2ML sized pumps used



**Q3251:** J. M. Muradov, *et al.* Intravenous Infusion of Magnesium Chloride Improves Epicenter Blood Flow during the Acute Stage of Contusive Spinal Cord Injury in Rats. *Journal of Neurotrauma* 2013;30(10):840-852

**Agents:** Magnesium chloride **Vehicle:** PEG; **Route:** IV (jugular); **Species:** Rat; **Pump:** 2001D; 1003D; 2001; **Duration:** 24 hours; 48 hours; 7 days;

**ALZET Comments:** Controls received mp w/ vehicle; animal info (female, Sprague Dawley, young adult, 180-220g); functionality of mp verified by residual volume; spinal cord injury; post op. care (Bacitracin ointment, saline injection SC, heating pad, twice daily bladder expression); behavioral testing (open field test, grid walk); Primed overnight in saline 37C

**Q3310:** J. L. McGuire, *et al.* Traits of fear resistance and susceptibility in an advanced intercross line. *European Journal of Neuroscience* 2013;38(9):3314-3324

**Agents:** Magnesium chloride **Vehicle:** Bicine buffer; **Route:** Not Stated; **Species:** Mice; **Pump:** 1003D; **Duration:** 3 days;

**ALZET Comments:** Controls received mp w/ vehicle; animal info (fear-susceptible or fear-resistant, 8-10 weeks old); behavioral testing (fear testing); MRI; manganese used to enhance MRI signal

**Q2320:** K. Mori, *et al.* Novel neuroprotective effect of cisternal and intra-cerebral magnesium sulfate solution infusion on delayed cerebral death in rat hippocampal neurons after transient global ischemia. *Brain Research* 2012;1480(1):72-80

**Agents:** Magnesium sulfate **Route:** CSF/CNS (cisterna magna); CSF/CNS (hippocampus); **Species:** Rat; **Pump:** 2ML2; 2001;

**ALZET Comments:** Animal info (Sprague Dawley, male)

**Q2356:** A. A. Korish. Magnesium sulfate therapy of preeclampsia: an old tool with new mechanism of action and prospect in management and prophylaxis. *HYPERTENSION RESEARCH* 2012;35(10):1005-1011

**Agents:** Magnesium sulfate **Vehicle:** Not Stated; **Route:** Not Stated; **Species:** Rat (pregnant); **Duration:** 6 days;

**ALZET Comments:** Control animals received mp w/ saline; animal info (Wistar, pregnant, nonpregnant female); 2ML sized pump used

**Q0444:** M. Ishii, *et al.* The effect of recombinant aminopeptidase A (APA) on hypertension in pregnant spontaneously hypertensive rats (SHRs). *Early Human Development* 2009;85(9):589-594

**Agents:** Magnesium sulfate **Vehicle:** Not Stated; **Route:** SC; **Species:** Rat (pregnant); **Pump:** Not Stated; **Duration:** 10 days;

**ALZET Comments:** Controls were not treated; animal info (pregnant SHRs, gestational day 5, 180-200 g, pregnant, WKYs, 220-240 g)

**P8623:** O. H. Khan, *et al.* Calcium antagonism in neonatal rats with kaolin-induced hydrocephalus. *Journal of Child Neurology* 2007;22(10):1161-1166

**Agents:** Magnesium chloride; MAfferent signalling through the common hepatic branch of the vagus inhibits voluntary food intake and modifies plasma metabolite levels in rats

magnesium sulfate **Vehicle:** **Route:** SC; **Species:** Rat (neonate); **Pump:** 2002; 2004; **Duration:** 14 days;

**ALZET Comments:** Controls received mp w/ saline, equimolar; dose-response (table 1); comparison of SC injections vs. mp; stress/adverse reaction : (see pg 1162) high magnesium sulfate concentrations led to necrosis and skin sloughing at implant site; animal info (Sprague-Dawley, P7); skin was closed with staples (wound clips used)

**P7889:** B. J. Coates, *et al.* MgSO<sub>4</sub> prevents left ventricular dysfunction in an animal model of preeclampsia. *American Journal of Obstetrics & Gynecology* 2006;195(5):1398-1403

**Agents:** L-NAME; magnesium sulfate **Vehicle:** Saline; **Route:** SC; **Species:** Rat (pregnant); **Pump:** 2ML1; **Duration:** 4 days;

**ALZET Comments:** Controls received mp w/ vehicle; cardiovascular; animal info (female, Sprague-Dawley, 150-175g.); "Infusion of L-NAME in pregnant rats represent an excellent animal model suitable for the study of cardiovascular dysfunction in preeclampsia." (pg. 1401)

**P4822:** H. Sameshima, *et al.* Long-term magnesium sulfate treatment as protection against hypoxic-ischemic brain injury in seven-day-old rats. *American Journal of Obstetrics & Gynecology* 2001;184(185-190)

**Agents:** Magnesium sulfate **Vehicle:** Not Stated; **Route:** SC; **Species:** Rat (neonate); **Pump:** 1003D; **Duration:** 3 days;

**ALZET Comments:** Controls received mp w/ saline; functionality of mp verified by measuring magnesium ion concentrations; teratology; seven-day old rat pups weighed on average 13.9 ± 2.5 grams; neuroprotection; ischemia (cerebral)



**P3074:** D. W. Zochodne, *et al.* A segmental chronic pain syndrome in rats associated with intrathecal infusion of NMDA: evidence for selective action in the dorsal horn. *Canadian Journal of Neurological Sciences* 1994;21(24-28

**Agents:** NMDA; Magnesium sulfate **Vehicle:** PBS; **Route:** CSF/CNS (intrathecal); **Species:** Rat; **Pump:** 2002; **Duration:** 4-8 weeks;

**ALZET Comments:** controls received mp with PBS; long-term study, pumps replaced every 2 weeks; NMDA given with MgSO4

**P3663:** S. Nag, *et al.* Spinal neuronal pathology associated with continuous intrathecal infusion of N-methyl-D-aspartate in the rat. *Acta Neuropathologica* 1990;81(7-13

**Agents:** NMDA; Glycine; Magnesium sulfate; APV **Vehicle:** PBS; **Route:** CSF/CNS (intrathecal); **Species:** Rat; **Pump:** Not Stated; **Duration:** 1, 2, or 4 weeks;

**ALZET Comments:** controls received no agent or mp w/ .1MPBS alone or w/ .15M glycine in .1MPS; 0.2 and 0.5M NMDA for 1-2 weeks poorly tolerated; .15M for 2 & 4 weeks better; NMDA and other agents infused in pairs

**P1235:** P. P. McCaslin, *et al.* Anticonvulsive activity of several excitatory amino acid antagonists against barbitol withdrawal-induced spontaneous convulsions. *European Journal of Pharmacology* 1988;147(381-386

**Agents:** Glutamyl diethyl ester; Magnesium sulfate; Piperidine dicarboxyl acid, cis-2,3-; Phosphonoheptanoic acid, 2-amino-7- **Vehicle:** Saline; **Route:** CSF/CNS; **Species:** Rat; **Pump:** 2001; **Duration:** 48 hours;

**ALZET Comments:** controls received mp w/saline; mp connected to cannula

### Manganese

**Q10173:** M. Grotell, *et al.* Alcohol Co-Administration Changes Mephedrone-Induced Alterations of Neuronal Activity. *Frontiers in Pharmacology* 2021;12(679759

**Agents:** Manganese chloride **Vehicle:** Saline, tris-buffered; **Route:** SC; **Species:** Rat; **Pump:** 2001; **Duration:** 7 days;

**ALZET Comments:** Dose: (120 mg/kg) Controls received mp w/ vehicle; animal info: Juvenile male Wistar rats (RccHan:WIST) post op. care: Carprofen (5 mg/kg), Manganese chloride aka (MnCl2)

**Q9872:** X. J. Zeng, *et al.* A2A R inhibition in alleviating spatial recognition memory impairment after TBI is associated with improvement in autophagic flux in RSC. *J Cell Mol Med* 2020;24(12):7000-7014

**Agents:** Manganese chloride **Vehicle:** Not Stated; **Route:** Abdomen; **Species:** Mice; **Pump:** 1007D; **Duration:** 7 days;

**ALZET Comments:** Dose (400 mg/kg); animal info (Male mice aged 8-12 weeks and weighing 22-26 g); behavioral testing (Y-maze test); Manganese chloride aka MnCl2; ischemia (Traumatic Brain Injury);

**Q10230:** R. Li, *et al.* Mapping accumulative whole-brain activities during environmental enrichment with manganese-enhanced magnetic resonance imaging. *Neuroimage* 2020;210(116588

**Agents:** Manganese chloride **Vehicle:** Saline; **Route:** IP; **Species:** Mice; **Pump:** 1007D; **Duration:** 7 days;

**ALZET Comments:** Controls received mp w/ vehicle; animal info: mice (about 8 weeks old 30.5-40.5 g); post op. care: followed by closure of the wound with surgical suture and disinfection with 75% ethanol; Manganese Chloride aka (MnCl2) immunology;

**Q8634:** R. Li, *et al.* Mapping accumulative whole-brain activities during environmental enrichment with manganese-enhanced magnetic resonance imaging. *NeuroImage* 2020;210(116588

**Agents:** Manganese chloride **Vehicle:** Saline; **Route:** Abdomen; **Species:** Mice; **Pump:** 1007D; **Duration:** 7 days;

**ALZET Comments:** Dose (100 mg MnCl2/kg); animal info (8 week old mice weighing 30.5-40.5 g); immunology;

**Q9172:** N. Cannella, *et al.* Cocaine addicted rats show reduced neural activity as revealed by manganese-enhanced MRI. *Scientific Reports* 2020;10(1):19353

**Agents:** Manganese Chloride **Vehicle:** Saline; **Route:** SC; **Species:** Rat; **Pump:** 2001; **Duration:** 4 days;

**ALZET Comments:** Dose (120 mg/kg); animal info (male Sprague Dawley rats); Manganese Chloride aka MnCl2; dependence;



**Q8756:** A. E. Vozenilek, *et al.* Absence of Nicotinamide Nucleotide Transhydrogenase in C57BL/6J Mice Exacerbates Experimental Atherosclerosis. *Journal of Vascular Research* 2018;55(2):98-110

**Agents:** Manganese Chloride **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Pump:** 1004; **Duration:** 15 days;

**ALZET Comments:** Dose (25, 50 mg/kg/day); Controls received mp w/ vehicle; animal info (10-12 weeks, male, B6129SF1/Tac); post op. care (2 mg/kg meloxicam for 3 days); behavioral testing (Morris Water Maze); comparison of IP injection vs mp; MRI; stress/adverse reaction: ("mice implanted with pumps swam more slowly on the first 2 days of training than the control animals. By day 3 this difference had normalized, and there was no effect of pumps, MnCl<sub>2</sub> treatment, or specific treatment group on swim speed." p.417. "Some mice that received MnCl<sub>2</sub> via osmotic pump developed skin ulceration where the solution was being released from the pump. In 4/17 cases, the ulceration was so severe that the mice had to be euthanized." p.417); "when mice are given 50 mg/kg/day MnCl<sub>2</sub> via osmotic pump, the useable imaging window is only from day 3 to day 5. The useable imaging window for mice receiving 25 mg/kg/day is approximately 3–14 days." p.419;

**Q7932:** D. A. Vousden, *et al.* Continuous manganese delivery via osmotic pumps for manganese-enhanced mouse MRI does not impair spatial learning but leads to skin ulceration. *Neuroimage* 2018;173(4):411-420

**Agents:** manganese chloride **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Pump:** 1004; **Duration:** 15 days;

**ALZET Comments:** Dose (25, 50 mg/kg/day); Controls received mp w/ vehicle; animal info (10-12 weeks, male, B6129SF1/Tac); post op. care (2 mg/kg meloxicam for 3 days); behavioral testing (Morris Water Maze); comparison of IP injection vs mp; MRI; stress/adverse reaction: ("mice implanted with pumps swam more slowly on the first 2 days of training than the control animals. By day 3 this difference had normalized, and there was no effect of pumps, MnCl<sub>2</sub> treatment, or specific treatment group on swim speed." p.417. "Some mice that received MnCl<sub>2</sub> via osmotic pump developed skin ulceration where the solution was being released from the pump. In 4/17 cases, the ulceration was so severe that the mice had to be euthanized." p.417); "when mice are given 50 mg/kg/day MnCl<sub>2</sub> via osmotic pump, the useable imaging window is only from day 3 to day 5. The useable imaging window for mice receiving 25 mg/kg/day is approximately 3–14 days." p.419;

**Q6745:** D. S. Poole, *et al.* Continuous infusion of manganese improves contrast and reduces side effects in manganese-enhanced magnetic resonance imaging studies. *Neuroimage* 2017;147(1-9)

**Agents:** Manganese Chloride **Vehicle:** PBS; **Route:** SC; **Species:** Mice; **Pump:** 1002; **Duration:** 8 days;

**ALZET Comments:** Dose (30 mg/kg and 60 mg/kg); Controls received mp w/ vehicle; animal info (10 week old C57BL/6J mice); comparison of IP injections vs mp; MRI; "Our study demonstrates that the osmotic pump is able to deliver Mn to the brain (and in a suitable amount) with contrast comparable to that achieved via IP injections. Although a higher dose does appear necessary to achieve a similar contrast, this higher dose administered via osmotic pump can be used without giving side effects. Additionally, the constant delivery of manganese ensures a stable blood level and presumably a more timing-independent manganese uptake during activation. Lastly, osmotic pump delivery ensures less animal handling during the experiment, which may be a large advantage for many studies involving behavior, fear or stress, where animal handling may have a large influence on the experimental outcome." pg.8 ;

**Q6080:** M. A. Laine, *et al.* Brain activation induced by chronic psychosocial stress in mice. *Sci Rep* 2017;7(1):15061

**Agents:** Manganese Chloride **Vehicle:** Saline, Tris-buffered; **Route:** SC; **Species:** Mice; **Pump:** 2002; **Duration:** 16 days;

**ALZET Comments:** Dose (160 mg/kg/week); animal info (male, C57BL/6NCrl, 5 weeks old); post op. care (SC injection of carprofen (5 mg/kg) for analgesia);

**Q6028:** I. M. Devonshire, *et al.* Manganese-enhanced magnetic resonance imaging depicts brain activity in models of acute and chronic pain: A new window to study experimental spontaneous pain? *Neuroimage* 2017;157(5):500-510

**Agents:** Manganese chloride **Vehicle:** Saline; **Route:** SC; **Species:** Rat; **Pump:** 2001; **Duration:** 14 days;

**ALZET Comments:** Controls received mp w/ vehicle; behavioral testing (voluntary wheel running); MRI-compatible polyetheretherketone tubing; Therapeutic indication (osteoarthritis, fmri); Dose (80 mg/kg);



**Q5421:** J. K. McCreary, *et al.* Altered brain morphology and functional connectivity reflect a vulnerable affective state after cumulative multigenerational stress in rats. *Neuroscience* 2016;330(79-89)

**Agents:** Manganese Chloride **Vehicle:** NaOH, TRIS-HCL buffer; **Route:** SC; **Species:** Rat (pregnant); **Pump:** 2001; **Duration:** 7 days;

**ALZET Comments:** Controls received mp w/ vehicle; animal info (120-day old MPS and non-stress control female Long-Evans rats); functionality of mp verified by plasma levels; no stress, "no toxic effects were anticipated or observed" (see pg. 81); behavioral testing (open-field exploration testing); MRI imaging every second day, total of 5 time points; Multigenerational prenatal stress model; stress response measured by plasma corticosterone levels and open-field exploration in each generation; MRI-compatible pumps used (PEEK); Dose (7.14 mg/kg);

**Q5342:** M. Dudek, *et al.* Alcohol preference and consumption are controlled by the caudal linear nucleus in alcohol-preferring rats. *European Journal of Neuroscience* 2016;43(11):1440-8

**Agents:** Manganese Chloride **Vehicle:** Saline, Tris-buffered; **Route:** SC; **Species:** Rat; **Pump:** 2001; **Duration:** 7 days;

**ALZET Comments:** animal info (male alcohol-preferring AA and male Wistar rats; 6 weeks old, 264-413 g); functionality of mp verified by MRI after pump removal; post op. care (carprofen injection); Dose (120 mg/kg/wk);

**Q5338:** T. Hoch, *et al.* Fat/carbohydrate ratio but not energy density determines snack food intake and activates brain reward areas. *Sci Rep* 2015;5(10041)

**Agents:** Manganese chloride **Vehicle:** Not Stated; **Route:** SC; **Species:** Rat; **Pump:** Not Stated; **Duration:** 7 days;

**ALZET Comments:** animal info (Wistar rats 571 +/-41 g); "To avoid negative side effects on basic physiology and behaviour of the animals due to the injection of the manganese chloride solution in doses sufficient for MEMRI measurement, osmotic pumps served for the gentle, but rather time-consuming continuous application of non-toxic amounts of manganese, which accumulated in the activated brain areas during the whole time course of the 7-day food test phase" (pg. 8); MRI use

**Q5142:** M. Dudek, *et al.* Brain activation induced by voluntary alcohol and saccharin drinking in rats assessed with manganese-enhanced magnetic resonance imaging. *Addiction Biology* 2015;20(6):1012-21

**Agents:** Manganese Chloride **Vehicle:** Saline, Tris-buffered; **Route:** SC; **Species:** Rat; **Pump:** 2001; **Duration:** 1 week;

**ALZET Comments:** animal info: male alcohol-preferring AA rats, 265–335 g; post op. care (subcutaneous injection of carprofen); MRI done after infusion; brain tissue distribution; brain Mn<sup>2+</sup> accumulation; Dose: 120 mg/kg/week

**Q4400:** B. den Hollander, *et al.* Manganese-Enhanced Magnetic Resonance Imaging Reveals Differential Long-Term Neuroadaptation After Methamphetamine and the Substituted Cathinone 4-Methylmethcathinone (Mephedrone). *INTERNATIONAL JOURNAL OF NEUROPSYCHOPHARMACOLOGY* 2015;18(U118-U126)

**Agents:** Manganese chloride **Vehicle:** Tris-buffered saline; **Route:** SC; **Species:** Rat; **Pump:** 2001; **Duration:** 7 days;

**ALZET Comments:** Animal info (Wistar, 6 weeks old); post op. care (SC injection carprofen 5 mg/kg); behavioral testing (locomotor activity, novel object recognition); MRI; pumps primed overnight in 37C saline;

**Q3603:** D. S. Poole, *et al.* Three-dimensional inversion recovery manganese-enhanced MRI of mouse brain using super-resolution reconstruction to visualize nuclei involved in higher brain function. *NMR IN BIOMEDICINE* 2014;27(749-759)

**Agents:** Manganese chloride **Vehicle:** Not Stated; **Route:** SC; **Species:** Mice; **Pump:** 1007D; **Duration:** 8 days;

**ALZET Comments:** MRI;

**Q5337:** T. Hoch, *et al.* Manganese-enhanced magnetic resonance imaging for mapping of whole brain activity patterns associated with the intake of snack food in ad libitum fed rats. *PLoS One* 2013;8(2):e55354

**Agents:** Manganese chloride **Vehicle:** Not Stated; **Route:** SC; **Species:** Rat; **Pump:** 2001; **Duration:** 7 days;

**ALZET Comments:** animal info (Wistar rats, 257 +/- 21 g); good methods (pumps were incubated in isotonic saline for 12 h previous to implantation); For the use in MRI, the stainless steel flow moderator was replaced by a PEEK micro medical tubing; "Osmotic pump-assisted MEMRI proved to be a promising technique for functional mapping of whole brain activity..." (pg 1); "MnCl<sub>2</sub> is administered by osmotic pumps, which slowly and continuously release the solution over a time period of up to seven days avoiding adverse effects on motor activity, but providing sufficient manganese accumulation for MRI analysis" (pg. 2); Dose (1 M solution);



**Q2077:** M. R. Sepulveda, *et al.* Evaluation of manganese uptake and toxicity in mouse brain during continuous MnCl<sub>2</sub> administration using osmotic pumps. *Contrast Media & Molecular Imaging* 2012;7(4):426-434

**Agents:** Manganese chloride **Vehicle:** Saline; **Route:** SC; **Species:** Mice; **Pump:** 2004; **Duration:** 12, 21 days;

**ALZET Comments:** Controls received mp w/ vehicle; animal info (Swiss, 2 mo old); MRI; comparison of SC injections vs SC mp; "The novel method presented in this study in mice, which is based on subcutaneously implanted mini-osmotic pumps filled with MnCl<sub>2</sub>, appears to be a better system for delivering the agent into the interstitial tissue compared with repeated agent injections." pg 429

**Q1855:** S. I. Mok, *et al.* Infusion-based manganese-enhanced MRI: a new imaging technique to visualize the mouse brain. *Brain Structure and Function* 2012;217(1):107-114

**Agents:** Manganese chloride **Vehicle:** Not Stated; **Route:** SC; **Species:** Mice; **Pump:** 1003D; 1007D; 1002; **Duration:** 3, 7, 14 days;

**ALZET Comments:** Animal info (Oxtr KO, wt, 22-30 g, age-matched adult); MRI

**Q5566:** S. Boretius, *et al.* Manganese-enhanced magnetic resonance imaging. *Methods Mol Biol* 2011;771(531-68

**Agents:** Manganese **Vehicle:** Not Stated; **Route:** Not Stated; **Species:** Rat; **Pump:** Not Stated; **Duration:** 48 hours;

**ALZET Comments:** "One approach may be the use of micro-osmotic pumps\ that constantly infuse manganese into a targeted brain area for a period of about 48 h" (p. 542); "A slow manganese release by micropumps... may be alternative approaches to reduce the acute manganese toxicity." (p. 558)

**Q1056:** O. Eschenko, *et al.* Mapping of functional brain activity in freely behaving rats during voluntary running using manganese-enhanced MRI: Implication for longitudinal studies. *Neuroimage* 2010;49(3):2544-2555

**Agents:** Manganese chloride **Vehicle:** Saline; **Route:** IP; **Species:** Rat; **Pump:** 2001; **Duration:** Not Stated;

**ALZET Comments:** Controls received mp w/ vehicle; animal info (male, Sprague Dawley, 250-300 g); comparison of SC and IP injections vs IP mp; post op. care (Fynadine Essex, Baytril); behavioral testing (running wheel); "The results of this experiment clearly demonstrate the advantage of systemic administration of MnCl<sub>2</sub> via osmotic pumps, which provide a long-lasting, continuous and slow release of Mn 2+ into intraperitoneal space... Such release rate likely is readily managed by homeostatic mechanisms, does not produce toxic effects, while allows reaching relatively high cumulative dose." pg 2550; "In contrast (to chronic infusion with ALZET pumps), a single s.c. or i.p. application of MnCl<sub>2</sub> in a dose range of 16 - 80 mg/kg resulted in abrupt and long-lasting toxic effects." pg 2552; " we find the osmotic pump-administration protocol described in the present study clearly advantageous for longitudinal behavioral studies." pg 2553

**P1436:** J. J. Liccione, *et al.* Manganese-mediated increase in the rat brain mitochondrial cytochrome P-450 and drug metabolism activity: susceptibility of the striatum. *J. Pharmacol. Exp. Ther* 1989;248(1):222-228

**Agents:** Manganese chloride **Vehicle:** Water; **Route:** SC; **Species:** Rat; **Pump:** Not Stated; **Duration:** 7 days;

**ALZET Comments:** controls received saline

**P1435:** J. J. Liccione, *et al.* Selective vulnerability of glutathione metabolism and cellular defense mechanisms in rat striatum to manganese. *J. Pharmacol. Exp. Ther* 1988;247(1):156-161

**Agents:** Manganese chloride **Vehicle:** Water; **Route:** SC; **Species:** Rat; **Pump:** Not Stated; **Duration:** 7 days;

**ALZET Comments:** controls received saline

**P1138:** M. C. Newland, *et al.* The clearance of manganese chloride in the primate. *Fundam. Appl. Toxicol* 1987;9(2):314-328

**Agents:** Manganese chloride; Radio-isotopes **Vehicle:** Radio-isotopes; **Route:** SC; **Species:** Monkey; **Pump:** Not Stated;

**Duration:** 6 weeks;

**ALZET Comments:** Pump model not stated; half-life; multiple pumps per animal (2); comparison of MnCl inhalation vs. mp infusion; stress/adverse reaction (necrosis, edema at mp site); pump replaced