



References on the Administration of Metals Using ALZET® Osmotic Pumps

1. Arsenate

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

ALZET Comments: Arsenate, sodium; Radio-isotopes; Arsenic-74 tracer; Water; Radio-isotopes; hamster (pregnant); 2001; 8 days; 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. *Environ. Res* 1986;40(372-379)

ALZET Comments: Arsenate, sodium; SC; hamster; 2001; 24, 48, 72, 168 hours; 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. *Environ. Res* 1985;37(2):425-432

ALZET Comments: Arsenate, sodium; Water; SC; hamster (pregnant); 2001; 6-9 days; teratogenicity; pumps primed in saline 4 hr prior to implant; dose-response data, 4 doses tested; advantage of mp model p.431.

2. 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;



3. 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

ALZET Comments: Tricine; EDTA, copper; EDTA, zinc; EDPA; EDTA, calcium; Saline; cresyl violet; CSF/CNS; Rat; 2001D; 12 hours; 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)

ALZET Comments: Copper chloride; Cupric nitrilotriacetate; Nitrilotriacetic acid; SC; Rat; 2001; 3,5 days; 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

ALZET Comments: Copper sulfate; Saline; SC; rabbit; 2ML4; no duration posted; 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

ALZET Comments: Copper sulfate; Saline; SC; rabbit; 2ML4; no duration posted; uveitis model.

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

ALZET Comments: Copper sulfate; Saline; SC; Rat; 7 days; controls received mp w/ saline.

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4. 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)

ALZET Comments: Desferrioxamine; Desferrioxamine, iron-saturated; Water, double-distilled; SC; Rat; 2ML1; 8 days; controls received mp w/ water.

5. 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

ALZET Comments: Magnesium sulfate; SC; Rat; 2ML1; 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)

ALZET Comments: Magnesium sulfate; SC; Rat (pregnant); 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



ALZET Comments: Magnesium chloride; PEG; IV (jugular); Rat; 2001D; 1003D; 2001; 24 hours; 48 hours; 7 days; 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

ALZET Comments: Magnesium chloride; Bicine buffer; Mice; 1003D; 3 days; 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(:):72-80

ALZET Comments: Magnesium sulfate; CSF/CNS; CSF/CNS (cisterna magna); CSF/CNS (hippocampus); Rat; 2ML2; 2001; Animal info (Sprague Dawley, male).

6. Manganese

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, MnCl₂ treatment, or specific treatment group on swim speed." p.417. "Some mice that received MnCl₂ 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 MnCl₂ 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);