

## **ICCVAM Evaluation of Use of Topical Anesthetics, Systemic Analgesics, and Humane Endpoints to Avoid or Minimize Pain and Distress in Ocular Toxicity Testing**

### **Relevant References**

#### ***Key General References***

Draize J, Woodard G, Calvery H. 1944. Methods for the study of irritation and toxicity of substances applied topically to the skin and mucous membranes. *J Pharmacol Exp Ther* 82:377-390.

EPA. 1998. Health Effects Test Guideline, OPPTS 870.2400 Acute Eye Irritation. EPA 712-C-98-195. U.S. Environmental Protection Agency: Washington, DC.

ICCVAM. 1997. Validation and Regulatory Acceptance of Toxicological Test Methods: A Report of the ad hoc Interagency Coordinating Committee on the Validation of Alternative Methods. NIH Publication No.: 97-3981. Research Triangle Park:National Institute of Environmental Health Sciences.

ICCVAM. 2003. ICCVAM Guidelines for the Nomination and Submission of New, Revised, and Alternative Test Methods. NIH Publication No: 03-4508. Research Triangle Park:National Institute of Environmental Health Sciences.

ICCVAM. 2006. ICCVAM Test Method Evaluation Report: In Vitro Ocular Toxicity Methods for Identifying Severe Irritants and Corrosives. NIH Publication No: 07-4517. Research Triangle Park:National Institute of Environmental Health Sciences.

National Research Council (NRC). 2009. Recognition and Alleviation of Pain in Laboratory Animals: A Report of the NRC Committee on Recognition and Alleviation of Pain in Laboratory Animals (Available <http://www.nap.edu/catalog/12526.html>).

OECD. 2002. Test guideline 405. Acute eye irritation/corrosion, adopted April 24, 2002. In: OECD Guidelines for Testing of Chemicals. OECD, Paris.

Spielmann H et al. 1996. Results of a Validation Study in Germany on Two In Vitro Alternatives to the Draize Eye Irritation Test, the HET-CAM Test and the 3T3 NRU Cytotoxicity Test. *ATLA* 24:741-858.

UN. 2007. Globally Harmonised System of Classification and Labelling of Chemicals (GHS). New York & Geneva:United Nations Publications.

#### ***Additional References Cited in Background Review Document***

Balls M, Botham PA, Bruner LH, Spielmann H. 1995. The EC/HO international validation study on alternatives to the Draize eye irritation test. *Toxicol In Vitro* 9:871- 929.

- Bartfield J, Holmes TJ, Raccio-Robak N. 1994. A comparison of proparacaine and tetracaine eye anesthetics. *Acad Emerg Med* 1:364-367.
- Budd K. 2002. Immunosuppressive effects induced by opioid analgesics. *International Monitor on Regional Anesthesia and Pain Management* 14:3-7.
- Budd K, Collett BJ. 2003. Old dog – new (ma)trix. *Br J Anaesth.* 90:722-724.
- Capner CA, Lascelles BD, Waterman-Pearson AE. 1999. Current British veterinary attitudes to perioperative analgesia for dogs. *Vet Rec* 145:95-99.
- Catterall W, Mackie K. 2001. Local anesthetics. In: Goodman and Gilman's *The Pharmacological Basis of Therapeutics* (Hardman JG, Limbird LE, Gilman AG, eds). 10th ed. New York:McGraw Hill, 687-731.
- Cowan A, Doxey JC, Harry EJR. 1977. The animal pharmacology of buprenorphine, and oripavine analgesic agent. *Br J Pharmacol* 60:547-554.
- CPSC. 1984. Animal Testing Policy. *Federal Register* 49:22522-22523.
- Cramlet SH, Jones EJ. 1976. *Aeromedical Review, Selected Topics in Laboratory Animal Medicine: Anesthesiology, Vol V.* Brooks Air Force Base, Texas:USAF School of Aerospace Medicine. 11.
- Dohoo SE, Dohoo IR. 1996. Factors influencing the postoperative use of analgesics in dogs and cats by Canadian veterinarians. *Can Vet J* 37:552-556.
- Dum JE, Herz A. 1981. In vivo receptor binding of the opiate partial agonist, buprenorphine, correlated with its agonistic and antagonistic action. *Br J Pharmacol* 74:627-633.
- Eriksen J, Jensen N-H, Kamp-Jensen M, Bjarnø H, Friis P, Brewster D. 1989. The systemic availability of buprenorphine administered by nasal spray. *J Pharm Pharmacol* 41:803-805.
- Flecknell PA. 1984. Relief of pain in laboratory animals. *Lab Anim* 18:147-160.
- Flecknell PA. 1991. Postoperative analgesia in rabbits and rodents. *Lab Anim* 20:34-37.
- Flecknell PA. 1995. Anaesthesia and analgesia for rodents and rabbits. In: *Handbook of Rodent and Rabbit Medicine* (Laber-Laird K, Swindle MM, Flecknell PA, eds). Newton, MA;Pergamon Press, 219-237.
- Flecknell PA. 1996. Post-operative care. In: *Laboratory Animal Anaesthesia.* 2nd Ed. London: Academic Press.
- Flecknell PA, Liles JH. 1990. Assessment of the analgesic action of opioid agonist-antagonists in the rabbit. *J Assoc Vet Anaesthetics* 17:24-29.

- Flecknell PA, Liles JH. 1992. Evaluation of locomotor activity and food and water consumption as a method of assessing postoperative pain in rodents. In: *Animal Pain* (Short CE, Van Poznak A, eds). New York:Churchill Livingstone. 482-488.
- Gettings S, Lordo R, Hintze K, Bagley D, Casterton P, Chudkowski M, et al. 1996. The CTFA evaluation of alternatives program: an evaluation of in vitro alternatives to the Draize primary eye irritation test. (Phase III) surfactant-based formulations. *Food Chem Toxic* 34:79-117.
- Grant RL, Acosta D. 1994. A digitized fluorescence imaging study on the effects of local anesthetics on cytosolic calcium and mitochondrial membrane potential in cultured rabbit corneal epithelial cells. *Toxicol Appl Pharmacol* 129:23-35.
- Hand CW, Sear J, Uppington MJ, Ball M, Moore RA. 1990. Buprenorphine disposition in patients with renal impairment: single and continuous dosing, with special reference to metabolites. *Br J Anaesth* 64:276-282.
- Hansen B. 1997. Through a glass darkly: using behavior to assess pain. *Seminars Vet Med Surg (Small Anim)* 12:61-74.
- Heel RC, Brogden RN, Speight RM, Avery GS. 1979. Buprenorphine: a review of its pharmacological properties and therapeutic efficacy. *Drugs*. 17:91-100
- Hendrix DVH, Brooks DE, Smith PJ, Gelatt TR, Whittaker C, Pellicane C, et al. 1995. Corneal stromal abscesses in the horse: a review of 24 cases. *Equine Vet J* 27:440-447.
- Hermanssen K, Pedersen LE, Olesen HO. 1986. The analgesic effect of buprenorphine, etorphine, and pethidine in the pig: a randomized double blind crossover study. *Acta Pharmacol Toxicol (Copenh)* 59:27-35.
- Hoskin PJ, Hanks GW. 1987. Opioid therapy in malignant disease. *Clin Anaesthesiology* 1:888-904.
- Hubbell JAE, Muir WW. 1996. Evaluation of a survey of the diplomats of the American College of Laboratory Animal Medicine on use of analgesic agents in animals used in biomedical research. *J Am Vet Med Assoc* 209:918-921.
- Joubert KE. 2001. The use of analgesic drugs by South African veterinarians. *J S Afr Vet Assoc* 72:57-60.
- Ketring KL. 1980. Differential diagnosis and clinical considerations of ocular pain. *Vet Clin North Amer Sm Anim Pract* 10:251-260.

- Kohn DF, Martin TE, Foley PL, Morris TM, Swindel MM, Vogler GA and Wixson SK. 2007. Guidelines for the assessment and management of pain in rodents and rabbits. *J. Am. Assoc. Lab. Anim. Sci.* 46:97-108.
- Lascelles BD, Capner CA, Waterman-Pearson AE. 1999. Current British veterinary attitudes to perioperative analgesia for cats and small mammals. *Vet Rec* 145:601-604.
- Lindhardt K, Ravn C, Gizurason S, Bechgaard E. 2000. Intranasal absorption of buprenorphine – in vivo bioavailability study in sheep. *Int J Pharm* 205:159-163.
- Lindhardt K, Bagger M, Andreasen KH, Bechgaard E. 2001. *Int J Pharm* 217:121-126.
- Mandell DC, Holt EH. 2005. Ophthalmic emergencies. *Vet Clin Small Anim* 35:455-480.
- Mendelson J, Upton RA, Everhart ET, Jacob P, Jones RT. 1997. Bioavailability of sublingual buprenorphine. *J Clin Pharmacol* 37:31-37.
- Moreira LB, Kasetsuwan N, Sanchez D, Shah SS, LaBree L, McDonnell. 1999. Toxicity of topical anesthetic agents to human keratocytes in vivo. *J Cataract Refract Surg* 25:975-980.
- National Research Council (NRC). 2009. Recognition and Alleviation of Pain in Laboratory Animals: A Report of the NRC Committee on Recognition and Alleviation of Pain in Laboratory Animals (Available <http://www.nap.edu/catalog/12526.html>).
- Nolan AM, Livingston A, Waterman A. 1987. Investigation of the antinociceptive activity of buprenorphine in sheep. *Br J Pharm* 92:527-533.
- OECD. 1987. Test guideline 405, Acute eye irritation/corrosion, adopted February 24, 1987. In *OECD Guidelines for Testing of Chemicals*. OECD, Paris.
- OECD. 2000. Guidance Document on the recognition, assessment, and use of clinical signs as humane endpoints for experimental animals used in safety evaluation, distributed December 21, 2000. OECD, Paris.
- Park I, Kim D, Song J, In CH, Jeong SW, Lee SH, et al. 2008. Buprederm™, a new transdermal delivery system of buprenorphine: pharmacokinetic, efficacy and skin irritation studies. *Pharm Res* 25:1052-1062.
- Rapuano CJ. 1990. Topical anesthetic abuse: a case report of bilateral corneal ring infiltrates. *J Ophthalmic Nurs Technol* 9:94-95.
- Roberts LJ II, Morrow JD. 2001. Analgesic-antipyretic and anti-inflammatory agents and drugs employed in the treatment of gout. In: Goodman and Gilman's *The Pharmacological Basis of Therapeutics*. (Hardman JG, Limbird LE, Gilman AG, eds). 10th ed. New York:McGraw Hill, 687-731.

- Roy SD, Roos E, Sharma K. 1994. Transdermal delivery of buprenorphine through cadaver skin. *J Pharm Sci* 83:126-130.
- Scott DHT, Arthur GR, Scott DB. 1980. Haemodynamic changes following buprenorphine and morphine. *Anaesthesia* 35:957-961.
- Scott J, Huskisson EC. 1976. Graphic representation of pain. *Pain* 2:175-184.
- Seabaugh VM, Chambers WA, Green S, Gupta, KC, Hill RN, Hurley PM et al. 1993. Use of ophthalmic topical anesthetics. *Fd Chem Toxic* 31:95-98.
- Sittl R. 2005. Transdermal buprenorphine in the treatment of chronic pain. *Expert Rev Neurother* 5:315-323.
- Smith LJ, Bentley E, Shih A, Miller PE. 2004. Systemic lidocaine infusion as an analgesic for intraocular surgery in dogs: a pilot study.
- Sorge J, Sittl R. 2004. Transdermal buprenorphine in the treatment of chronic pain: Results of a Phase III, multicenter, randomized, double-blind, placebo-controlled study. *Clin Ther* 26:1808-1820.
- Trevithick JR, Dzialoszynski T, Hirst M, Cullen AP. 1989. Esthesiometric evaluations of corneal anesthesia and prolonged analgesia in rabbits. *Lens Eye Tox Res* 6:387-393.
- Watanabe K, Yakou S, Takayama K, Isowa K, Nagai T. 1996. Rectal absorption and mucosal irritation of rectal gels containing buprenorphine hydrochloride prepared with water-soluble dietary fibers, xanthan gum and locust bean gum. *J Control Release* 38:29-37.
- Watson AD, Nicholson A, Church DB, Pearson MR. 1996. Use of anti-inflammatory and analgesic drugs in dogs and cats. *Aust Vet J* 74:203-210.
- Wilson RP. 1990. Anesthesia. In: *Ophthalmic Surgery Principles & Practice* (Spaeth GL, ed). 2nd ed. Philadelphia:WB Saunders, 75-99.
- Wright EM, Marcella KL, Woodson JF. 1985. Animal pain: evaluation and control. *Lab Animal*. May/June:20-36.
- Zagelbaum BM, Tostanoski JR, Hochman MA, Hersh PS. 1994. Topical lidocaine and proparacaine abuse. *Am J Emerg Med* 12:96-97.

***Additional References Cited in Background Review Document Appendix A***

- BLS. 2003. U.S. Department of Labor, Bureau of Labor Statistics Annual Survey of Occupational Injuries and Illnesses (BLS-SOII). Bureau of Labor Statistics (<http://www.bls.gov>) [accessed 01 Nov 2005].

EPA. 1996. Label review manual. 2nd Edition. EPA737-B-96-001. Washington, DC: U.S. Environmental Protection Agency.

EU. 2001. Commission Directive 2001/59/EC of 6 August 2001 adapting to technical progress for the 28th time Council Directive 67/548/EEC on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances. Official Journal of the European Communities L255:1-333.

FDA. 1938. Food, Drug and Cosmetic Act of 1938. Public Law 75-717.

Nussenblatt RB, Bron A, Chambers W, McCulley, JP, Pericoi M, Ubels JL, Edelhauser, HF, Porter, L. 1998. Ophthalmologic perspectives on eye irritation testing. J Toxicol Cutaneous and Ocular Toxicol 17: 103-109.

OECD. 2002. Test guideline 405. Acute eye irritation/corrosion, adopted April 24, 2002. In: OECD Guidelines for Testing of Chemicals. OECD, Paris.

Wilhelmus KR. 2001. The Draize Eye Test. Surv Ophthalm. 45:493-515.

***Additional References Cited in Background Review Document Appendix A***

Anonymous. Anesthetics for Draize: follow-up. 1981. Int J Stud Anim Probl 2:174.

Arthur BH, Kennedy GL, Pennisi SC, North-Root H, Dipasquale LC, Penny DA, et al. 1986. Effects of anesthetic pretreatment and low volume dosage on ocular irritancy potential of cosmetics: a collaborative study. J Toxicol Cutaneous Ocul Toxicol 5:215-227.

DOL. 2004. Bureau of Labor Statistics, Case and Demographic Characteristics for Work-related Injuries and Illnesses Involving Days Away From Work. (Webpage on DOL website)

Durham RA, Sawyer DC, Keller WF, Wheeler CA. 1992. Topical ocular anesthetics in ocular irritancy testing: a review. Lab Anim Sci 42:535-541.

EPA. 2005a. Good Laboratory Practice Standards. Federal Insecticide, Fungicide, and Rodenticide Act. 40CFR160.

EPA. 2005b. Good Laboratory Practice Standards. Toxic Substances Control Act. 40CFR792. (Webpage on EPA website)

EU. 2001. Commission Directive 2001/59/EC. Official J European Communities L255:1-333.

FDA. 2003. Good laboratory practice for nonclinical laboratory studies. 21CFR58.

Heywood R, James RW. 1978. Towards objectivity in the assessment of eye irritation. J Soc Cosmet Chem 29:25-29.

Johnson AW. 1980. Use of small dosage and corneal anaesthetic for eye testing in vivo. In: Proceedings of the CTFA Ocular Safety Testing Workshop: In Vivo and In Vitro Approaches. October 6-7, 1980, Washington, DC. Washington, DC:Cosmetic, Toiletries, and Fragrance Association.

NIOSH. 2004. Work-Related Injury Statistics Query System. NIOSH. (Webpage on CDC website)

Rowan AN, Goldberg AM. 1985. Perspectives on alternatives to current animal testing techniques in preclinical toxicology. *Ann Rev Pharmacol Toxicol* 25:225-247.

Siegel SN, Castellan NJ. 1956. Nonparametric statistics for the behavioral sciences. 1st ed. New York:McGraw-Hill.

Ulsamer AG, Wright PL, Osterberg RE. 1977. A comparison of the effects of model irritants on anesthetized and nonanesthetized rabbit eyes. Abstract 143. Society of Toxicology Abstracts 177.

Walberg J. 1983. Exfoliative cytology as a refinement of the Draize eye irritancy test. *Toxicol Lett* 18:49-55.

***Additional References on The Effects of Topical Anesthetics on the Spontaneous Blink Reflex***

Maurice D. 1995. The effect of the low blink rate in rabbits on topical drug penetration. *J Ocular Pharmacology and Therapeutics* 11:297-304.

Naase T, Doughty MJ, Button NF. 2005. An assessment of the pattern of spontaneous eyeblink activity under the influence of topical ocular anaesthesia. *Graefe's Arch Clin Exp Ophthalmol* 243:306-312.

Schwartz DM, Fields HL, Duncan KG, Duncan JL, Jones MR. 1998. Experimental study of tetrodotoxin, a long-acting topical anesthetic. *Am J Ophthalmology* 125:481-487.

***Additional References on the Effects of Nonsteroidal Anti-inflammatory Drugs (NSAIDs) on Rabbit Eye Wound Healing***

Hersh PS, Rice BA, Baer JC, Wells PA, Lynch SE, McGuigan LJB, et al. 1990. Topical nonsteroidal agents and corneal wound healing. *Arch Ophthalmol* 108:577-583.

Kaji Y, Amano S, Oshika T, Obata H, Ohashi T, Sakai H, et al. 2000. Effect of anti-inflammatory agents on corneal wound-healing process after surface excimer laser keratectomy. *J Cataract Refract Surg* 26:426-431.

Lee BP, Kupferman A, Leibowitz HM. 1985. Effect of suprofen on corneal wound healing. *Arch Ophthalmol* 103:95-97.

Loya N, Bassage S, Vyas S, del Cerro M, Park SB, Aquavella JV. 1994. Topical diclofenac following excimer laser: effect on corneal sensitivity and wound healing in rabbits. *J Refractive Corneal Surgery* 10:423-427.

Miller D, Gruenberg P, Miller R, Bergamini MVW. 1981. Topical flurbiprofen or prednisolone: effect on corneal wound healing in rabbits. *Arch Ophthalmol* 99:681-682.

Nassaralla B, Szerenyi K, Wang XW, Reaves TA, McDonnell PJ. 1995. Effect of diclofenac on corneal haze after photorefractive keratectomy in rabbits. *Ophthalmology* 102:469-474.

Park SC, Kim JH. 1996. Effect of steroids and nonsteroidal anti-inflammatory agents on stromal wound healing following excimer laser keratectomy in rabbits. *Ophthalmic Surg Lasers* 27:S481-S486.