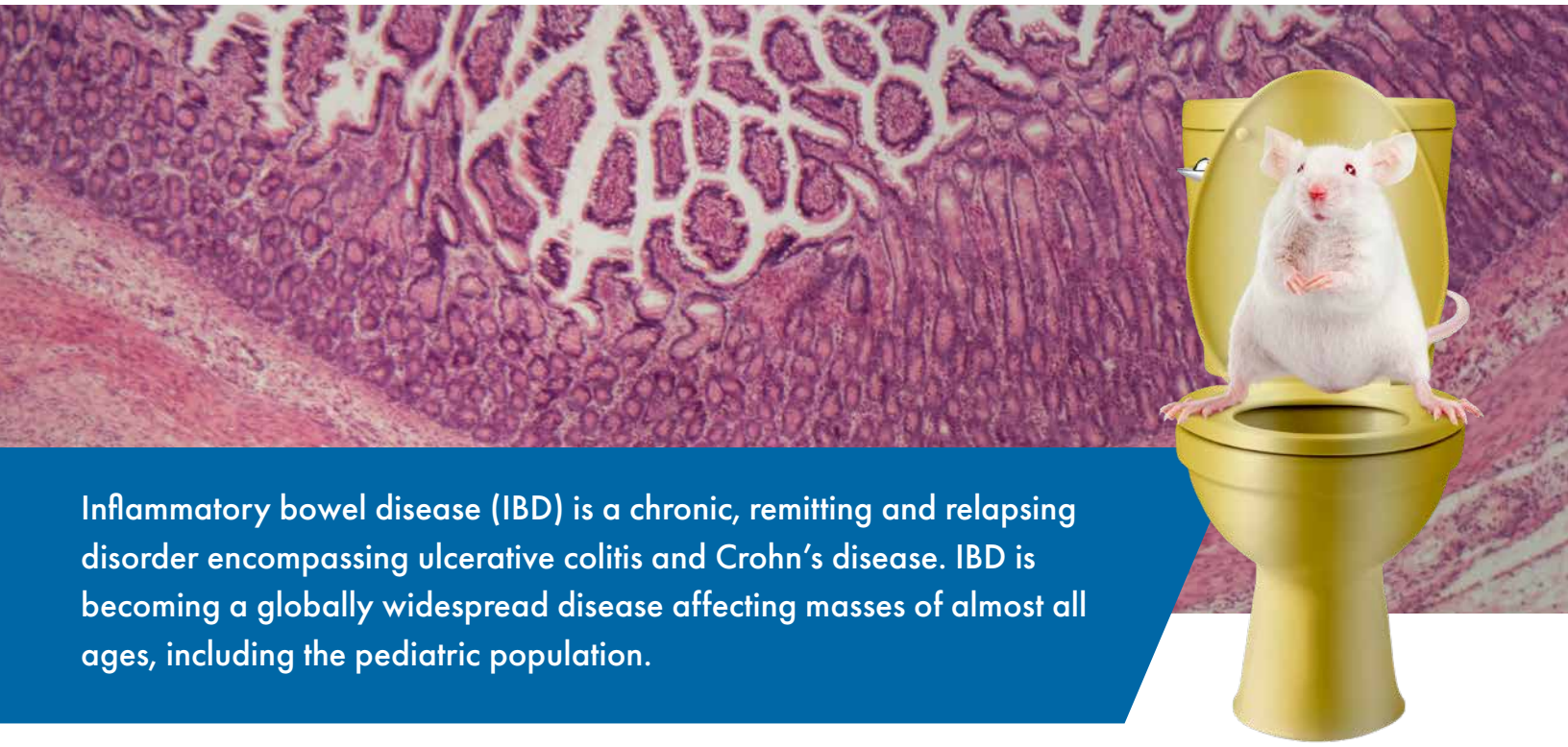
APPLICATION NOTES

Dextran Sodium Sulfate for Colitis Animal Model Research



Inflammatory bowel disease (IBD) is a chronic, remitting and relapsing disorder encompassing ulcerative colitis and Crohn's disease. IBD is becoming a globally widespread disease affecting masses of almost all ages, including the pediatric population.

Clinically, IBD is characterized by severe diarrhea, bleeding, abdominal pain, fluid and electrolyte loss, reflecting an underlying inflammatory process. Crohn's disease can affect any part of the gastrointestinal tract, but the most commonly affected areas include the terminal ileum or the perianal region. Specifically, Crohn's disease is characterized by significant thickening of the submucosal layer of the bowel wall. In ulcerative colitis (UC), inflammation can be observed in the mucosal layer of the large intestine.

IBD disease results from a defect with the mucosal immune system. Over the past several decades, dozens of different animal models have been developed to study IBD. These models can be broadly divided into spontaneous colitis models, inducible colitis models, genetically modified models and adoptive transfer models.

Although these models do not represent the complexity of human disease, they are valuable and indispensable tools. The models provide a wide range of options for investigating the involvement of various factors into the pathogenesis of IBD and help evaluate different therapeutic options.

Chemically induced murine models of intestinal inflammation are one of the most commonly used models because they are simple to induce and the onset, duration and severity of inflammation are immediate and controllable.

Both dextran sodium sulfate (DSS) and trinitrobenzene sulfonic acid (TNBS-) induced colitis are well-established animal models of mucosal inflammation that have been used for over 2 decades in preclinical studies and to study IBD pathogenesis.

DSS causes erosions with complete loss of surface epithelium because of its direct toxic effect on epithelial cells. It causes deformity in epithelial integrity, thereby increasing colonic mucosal permeability. This allows for permeation of large molecules with molecular weights up to 50 kDa, including DSS.

The DSS-induced colitis model has some advantages when compared to other animal models of colitis. For example, an acute, chronic, or relapsing model can easily be generated by changing the concentration of the administered DSS (and cycle in rats and other strains of mice). Moreover, dysplasia that resembles the clinical course of human UC occurs frequently in the chronic phase of DSS-induced colitis. DSS-induced model for studying colitis-associated carcinogenesis has been recently reviewed by others.

Studies validating DSS models using various therapeutic agents for human IBD have shown that DSS-induced colitis can be used as a relevant model for the translation of mice data to human disease. The following tables provide DSS dosage recommendations for various animal models based on published literature.

Dosage of DSS for different strains of mice

Animal/Strain	Dose	Days	Publication
C57BL/6	2.5%	8	Jia, Q.; Ivanov, I.; Zlatev, Z.; et al. Dietary fish oil and curcumin combine to modulate colonic cytokinetics and gene expression in dextran sodium sulphate-treated mice. *Br.J.Nutr.* **2011**, *106(4)*, 519-9.
Wild-type C57BL/6J(m)	3%	6	Thiess, A.L.; Laroui, H.; Obertone, T.S.; et al. Nanoparticle-based therapeutic delivery of prohibitin to the colonic epithelial cells ameliorates acute murine colitis. *Inflamm. Bowel Dis.* **2011**, *17(5)*, 1163-76.
C57BL/6 AhR null, WT	3.5%	7	Arsenescu, R.; Arsenescu, V.; Zhong, J.; et al. Role of xenobiotic receptor in inflammatory bowel disease. *Inflamm. Bowel Dis.* **2011**, *17(5)*, 1149-2.
C57BL/6	5%	3-14	Nagalingham, N.A.; Kao, J.Y.; Young, V.B. Microbial ecology of the murine gut associated with the development of dextran sodium sulfate-induced colitis. *Inflamm, Bowel Disease.* **2011**, *7(4)*, 917-26.
C57BL/6	1.5%	7	Ramakers, J.; Verstege, M.I.; Thuijls, G.; et al. The PPARγ agonist rosiglitazone impairs colonic inflammation in mice with experimental colitis. *J.Clin.Immunol.* **2007**, *27(3)*, 275-283.
BALB/c	1%	10	Palffy, R.; Gardlik, R.; Behuliak, M.; et al. Salmonella-mediated gene therapy in experimental colitis in mice. *Ex.Biol.Med.* **2011**, *236(2)*, 177-83.
C57BL/6J	3%	5	Shiomi, Y.; Nishiumi, S.; Ooi, M.; et al. GCMS-based metabolomic study in mice with colitis induced by dextran sulfate sodium. *Inflamm. Bowel Dis.* **2011**, *17(11)*, 2261-74.
BALB/c	1-5%	10	Rochat, T.; Bermudez-Humaran, L.; Gratadoux, J-J.; et al. Anti-infammatory effects of Lactobacillus casei BL23 producing or not a manganese-dependent catalase on DSS-induced colitis in mice. *Microb. CellFact.* **2007**, *20(6)*, 22.
BALB/c; NMRI/KI	2.5-5%	n/a	Bylund-Fellenius, A-C.; Landström, E.; Axelsson, L.G.; et al. Experimental colitis induced by dextran sulphate in normal and germfree mice. *Microbial Ecology in Health and Disease.* **1994**, *7*, 207-215.
IL-5-/- and +/+	2.9%, 5%	9	Stevceva, L.; Pavli, P.; Husband, A.; et al. Eosinophilia is attenuated in experimental colitis induced in IL-5 deficient mice. *Genes Immun.* **2000**, *1(3)*, 213-8.
BALB/c; athymic nu/nu CD-1 (BR)	2.5-5%	7-35	Axelsson, L.G.; Landström, E.; Bylund-Fellenius, A.C. Experimental colitis induced by dextran sulphate sodium in mice: Beneficial effects of sulphasalazine and olsalazine. *Aliment. Pharmacol.Ther.* **1998**, *12(9)*, 925-34.
WT; CCR9(-/-); CCL25 (-/-)	2%	7	Wurbel, M.A.; McIntyre, M.G.; Dwyer, P.; et al. CCL25/CCR9 interactions regulate large intestinal inflammation in a murine model of acute colitis. *PLoS One.* **2011**, *6(1)*, e16442.
Wild-type; DPIV -/-	2%	6	Yazbeck, R.; Howard, G.S.; Butler, R.N.; et al. Biochemical and histological changes in the small intestine of mice with dextran sulfate sodium induced colitis. *J.Cell Physiol.* **2011**, *226(12)*, 319-24.
BALB/c	5%	7	Kumar, G.K.; Dhamotharan, R.; Kulkarni, N.M. Embelin ameliorates dextran sodium sulfate-induced colitis in mice. *Int. Immunopharmacol.* **2011**, E

Dosage of DSS for different strains of rats

Animal/Strain	Dose	Days	Publications
Wistar	2%	2 weeks to 6 months	Tamaru, T.; Kobayashi, H.; Kishimoto, S.; et al. Histochemical study of colonic cancer in experimental colitis of rats. *Dig. Dis. Sci.* **1993**, *38*, 529-537.
Sprague-Dawley	5%	9	Schreiber, O.; Petersson, J.; Phillipson, M.; et al. Lactobacillus reuteri prevents colitis by reducing P-selectin associated leukocyte- and platelet-endothelial cell interactions. *Am.J.Physiol.Gastrointest.Liver.* **2009**, *296*, G534-542. Dicksved, J.; Schreiber, O.; Willing, B.; et al. Lactobacillus reuteri maintains a functional mucosal barrier during DSS treatment despite mucus layer dysfunction. *PLoS One.* **2012**, *7(9)*, e46399. Petersson, J.; Schreiber, O.; Steege, A.; et al. eNOS involved in colitis-induced mucosal blood flow increase. *Am.J.Physiol.Gastrointest.Liver.* **2007**, *293*, G1281-1287.
Sprague-Dawley	5%	6	Vasina, V.; Broccoli, M.; Ursino, M.G.; et al. Non-peptidyl low molecular weight radical scavenger IAC attenuates DSS-induced colitis in rats. *World J.Gastroenterol.* **2010**, *16(29)*, 3642-50.
Sprague-Dawley	5%	7	Shi, X.Z.; Winston, J.H.; Sarna, S.K. Differential immune and genetic responses in rat models of Crohn's colitis and ulcerative colitis. *Am.J.Physiol.Gastrointest.Liver Physiol.* **2011**, *300(1)*, G41-51.
Wistar	2.5%	7	Aoi, Y.; Terashima, S.; Ogura M.; et al. Roles of nitric oxide (NO) and NO synthases in healing of dextran sulfate sodium-induced rat colitis. *J Physio Pharmacol.* **2008**, *59(2)*, 315-36.
Wistar	5%	10	Lopez-Posadeas, R.; Requena, P.; Gonzalez, R.; et al. Bovine glycomacropeptide has intestinal antiinflammatory effects in rats with dextran-sulfate induced colitis. *J.Nutr.* **2010**, *140(11)*, 2014-2019.
Wistar	2-4%	7	Shimizu, T.; Suzuki, M.; Fujimura, J.; et al. The relationship between the concentration of dextran sodium sulfate and the degree of induced experimental colitis in weanling rats. *J.Pediatric Gastro. Nutrition.* **2003**, *37*, 481-486.
ACI	5%	14	Hirono, I.; Kuhara, K.; Hosaka, S.; et al. Induction of intestinal tumors in rats by dextran sulfate sodium. *J.Natl.Cancer Inst.* **1981**, *66(3)*, 579-583.

Dosage of DSS for other animals

Animal/Strain	Dose	Days	Publications
Hamster	2.5%	6	Karlsson, A.; Jägervall, A.; Pettersson, M.; et al. Dextran sulphate sodium induces acute colitis and alters hepatic function in hamsters. *Int. Immunopharmacol.* **2008**, *8(1)*, 20-27.
Hamster	1%	n/a	Yamada, M.; Ohkusa, T.; Ohkusa, I. Occurence of dysplasia and adenocarcinoma after experimental chronic ulcerative colitis in hamsters induced by dextran sulphate sodium. *Gut.* **1992**, *33*, 1521-1527.
Guinea Pig	3%	4	Iwanaga, T.; Hoshi, O.; Han, H.; et al. Morphological analysis of acute ulcerative colitis experimentally induced by dextran sulfate sodium in the guinea pig: Some possible mechanisms of cecal ulceration. *J. Gastroenterol.* **1994**, *29(4)*, 430-438.
Pig (Yorkshire)	1.25 g/kg BW	5	Young, D.; Ibuki, M.; Nakamori, T.; et al. Soy-derived di-and tripeptides alleviate colon and ileum inflammation in pigs with dextran sodium sulfate-induced colitis. *J.Nutr.* **2012**, *142(2)*, 363-8.

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