# Scientific Summary for Dexamethasone/Betamethasone Environmental Substance Proposed Model Rule

Dexamethasone (DXM) sodium phosphate is a widely used corticosteroid for inflammatory conditions in horses, regulated in racing jurisdictions in the United States by a 0.005 ng/mL serum/plasma threshold. We conducted a study to describe serum concentrations of DXM at 48 and 72 hours after intravenous administration of 20 mg DXM sodium phosphate to Thoroughbreds, Standardbreds and Quarter Horses (total horses = 75).[1] The majority of horses followed the expected pharmacokinetics, but one horse had an unexpectedly high serum concentration of 40 pg/mL at 48 hours, and 2 other horses had unexpectedly high serum concentrations of 10 pg/mL and 95 pg/mL at 72 hours. To investigate the possibility of environmental exposure and inadvertent transfer from the stall, we collected urine from one horse administered dexamethasone, put 100mL of this urine on hay and offered the hay to 6 experimental horses. All 6 horses had detectable serum dexamethasone during the following 24 hours, with one horse testing positive for dexamethasone at two different time points. This demonstrated that horses readily will test positive for dexamethasone from urine contamination of the hay.

Likely environmental contamination and transfer has been observed in other pharmacokinetic studies conducted with dexamethasone in experimental horses. A summary is presented in the following table:

| Study | Time (h) | Number of Unexpected high Concentration | Concentration (pg/mL) |
|---|---|---|---|
| Soma et al., 2005[2] | 48 | 2 | 600, 700 |
| Soma et al., 2013[3] | 48 | 1 | 57 |
| Symonds et al., 2019[4] | 96 | 1 | 100 |

In order to consider a higher threshold than is currently in place, a consideration of any relevant effect that this level of drug might have on the athlete is required. In a study evaluating experimentally induced lameness, where dexamethasone was introduced into the joint, the lowest blood concentration of dexamethasone associated with improved lameness score was 300 pg/mL.[5] Other studies have evaluated

[1] McClure S, Fenger C, Kersh K, Brown B, Maylin G, Duer W, Dirikolu L, Brewer K, Machin J, Tobin T. 2020. Dexamethasone serum concentrations after intravenous administration in horses during race training. *Comparative Exercise Physiology,* In Press.

[2] Soma LR, Uboh CE, Luo Y, Guan F, Moate PJ, Boston RC. 2005. Pharmacokinetics of dexamethasone with pharmacokinetic/pharmacodynamic model of the effect of dexamethasone on endogenous hydrocortisone and cortisone in the horse. *J Vet Pharmacol Therap* 28: 71–80.

[3] Soma LR, Uboh CE, Liu Y, Li X, Robinson MA, Boston RC, Colahan PT. 2013. Pharmacokinetics of dexamethasone following intra-articular, intravenous, intramuscular, and oral administration in horses and its effects on endogenous hydrocortisone. *J Vet Pharmacol Ther* 36(2):181-91.

[4] Symonds NE, Dart AJ, Keledjian J, Liu Lau M, Ennis LC, McIver VC, Tsang AS, Biasutti SA, Jeffcott LB. 2019. Pilot study to quantify the time to clear dexamethasone from plasma and urine of adult horses following a single nebulization. *Aust Vet J* 97: 144-148.

[5] Ekstrand C, Bondesson U, Giving E, Hedeland M, Ingvast-Larsson C, Jacobsen S, Löfgren M, Moen L, Rhodin M, Saetra T, Ranheim B. 2019. Disposition and effect of intra-articularly administered dexamethasone on lipopolysaccharide induced equine synovitis. *Act Vet Scand* 61:28.

the dexamethasone suppression of endogenous cortisol, which is measurable at blood concentrations as low as 7 pg/mL, and a prolonged effect, when an *ex vivo* (meaning manipulation of cells after removal from the animal) model is used.[6] However, the authors present no evidence to support any relationship between a relevant clinical effect and these *ex vivo* data.

In the absence of any data to support an effect on performance or masking of lameness below 300 pg/mL, and with clear evidence that concentrations at and below 100 pg/mL occur relatively commonly (1 in 50 horses at risk[1])as a result of inadvertent environmental contamination, this Model Rule proposal produces no risk to the integrity of horse racing, and solves the problem of inadvertent environmental transfer of dexamethasone. Betamethasone is included in the same proposal because it is a stereoisomer of dexamethasone and therefore behaves in the same fashion.

Further, this proposal establishes an ARCI category and penalty structure for Environmental Substances, a first step in addressing the problem of transfer of substances in the environment of the horse causing positive tests well beyond the control of any horseman, and threatening the entire industry by publicity conflating environmental contamination with "doping".

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[6] Knych HK, Weiner D, Arthur RM, Baden R, McKemie DS, Kass PH. 2020. Serum concentrations, pharmacokinetic/pharmacodynamic modeling, and effects of dexamethasone on inflammatory mediators following intravenous and oral administration to exercised horses. *Drug Test Anal* 12(8):1087-1101.