日本香粧品学会誌　Vol. 49, No. 4, pp. 264–274（2025）

〈一般論文〉

医薬部外品申請における Next Generation Risk Assessment（NGRA）の活用に向けた事例研究
—リードアクロスによる2-Isobutoxyethanolの発生毒性予測—

久木友花[1,*]，関根秀一[1]，田村亜紀子[1]，中川翔太[2]，額田祐子[2]，
齋藤和智[2]，小野　敦[3]，棗形麻樹子[4]，廣田衛彦[5]，豊田明美[5]，
畑尾正人[5]，高橋祐次[6]，足利太可雄[7]，山田隆志[6]

A Case Study for Utilization of Next Generation Risk Assessment (NGRA) for the Approval of Quasi-Drugs: Predicting the Developmental Toxicity of 2-Isobutoxyethanol with Read-Across

Tomoka HISAKI[1,*], Shuichi SEKINE[1], Akiko TAMURA[1], Shota NAKAGAWA[2], Yuko NUKADA[2], Kazutoshi SAITO[2], Atsushi ONO[3], Makiko KUWAGATA[4], Morihiko HIROTA[5], Akemi TOYODA[5], Masato HATAO[5], Yuji TAKAHASHI[6], Takao ASHIKAGA[7], Takashi YAMADA[6]

(Accepted: October 6, 2025)

Abstract

The evaluation of repeated dose toxicity and reproductive and developmental toxicity is required in domestic quasi-drug applications. However, due to the lack of clearly established animal testing alternatives, it is practically challenging to apply for new active ingredients in quasi-drugs without using animal testing. To address this, a research group was established with the aim of systematizing evaluation methods utilizing read-across as a promising alternative assessment method and promoting its acceptance in quasi-drug submissions. The group developed and reviewed two case studies.

In the second case study, 2-Isobutoxyethanol was selected as the target compound. The objective of this study was to predict the toxicity of 2-Isobutoxyethanol on maternal and embryo-fetal development following oral administration, based on information from nine selected analogs. During the comparison of similarities using various parameters, it was thought that the formation of alkoxyacetic acid through metabolism could be closely related to the adverse outcome pathway. Therefore, metabolic similarity was also examined. As a result, it was estimated that the toxicity of the target compound on embryo-fetal development is minimal. On the other hand, observations of analogs in maternal animals were mostly related to anemia caused by alkoxyacetic acid, and similar findings were anticipated for the target compound. Consequently, the lowest NOAEL among the similar compounds, 4 mg/kg/day (maternal) and 6.1 mg/kg/day (embryo-fetal), was estimated as the NOAEL for the target compound. Although direct comparison was not possible due to differences in test methods, the NOAEL for embryo-fetal development of the target compound was within the range of that of the analogs. As a result, it was determined that a conservative safety assessment was possible for the developmental toxicity of the target.

Subsequently, the contents of this case study were discussed with relevant experts from the industry, government, and academia. The final section of this paper organizes and presents the issues and key points discussed regarding the administrative acceptance of read-across.

Key words: read-across, developmental toxicity, quasi-drug applications, NGRA, 2-Isobutoxyethanol.