Vaginal Irritation Models: The Current Status of Available Alternative and In Vitro Tests

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Summary — Mucosal surfaces, such as the vaginal epithelium, are natural barriers to infection that are constantly exposed to bacteria and viruses, and are therefore potential sites of entry for numerous pathogens. The vaginal epithelium can be damaged mechanically, e.g. by the incorrect use of objects such as tampons, and by chemicals that are irritating or corrosive. Consequently, this can lead to an increase in susceptibility to further damage or infection. Pharmaceutical, cosmetic and personal care products that are specifically formulated for application onto human external mucosae can occasionally induce undesirable local or systemic side-effects. Therefore, the compatibility of applied materials with this mucosal surface represents a key issue to be addressed by manufacturers. The most frequently used method for assessing vaginal mucosal irritation is the in vivo rabbit vaginal irritation test. However, the current emphasis in the field of toxicology is to use alternative in vitro methods that reduce, refine, and replace the use of animals, and which model and predict human, not animal, responses. Such an approach is of particular interest to the personal care and cosmetic industries in their effort to comply with European legislative measures, such as the 7th Amendment to the EU Cosmetics Directive that does not permit the marketing of cosmetic products if they, or their ingredients, have been tested for irritation responses in animals. The focus of this review is to provide an overview of the alternative and in vitro tests that are currently available for vaginal mucosal irritation assessment, and which are already used, or may become useful, to establish the safety of newly-designed products for human use.

Key words: alternatives to animal testing, in vitro assays, vaginal irritation.

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Introduction

The vaginal mucosa represents one of the body’s host defence and immune surveillance components, providing an effective barrier against numerous pathogens. However, minor injuries may occur, following the use of feminine-care and cosmetic products, contraceptives or microbicides, which can induce irritation of the tissue and make the vaginal epithelium particularly susceptible to various types of infection. Therefore, it is important that the compatibility with the human mucosal surface of newly-developed cosmetic or personal care products, or of topically-applied drugs, is assessed before the product is launched.

Microbicides, for example, are designed to prevent infection by the human immunodeficiency virus (HIV) or other sexually transmitted infections. There are specific safety concerns regarding new microbicide formulations, in part due to the unexpected findings in recent clinical trials on the potential utility of nonoxynol-9 (N-9) as a microbicidal potency in a large-scale phase III trial (1), the low dose of N-9 gel (3.5%) increased a woman’s risk of HIV infection instead of reducing it, when used more than three and a half times per day. A major reason for this unexpected increase is thought to be the penetration of the virus into the vaginal epithelium resulting from vaginal irritation caused by N-9.

The current preclinical test for the assessment of vaginal irritation required by the US Food and Drug Administration (FDA) for the regulation of spermicides and microbicides (regulated as drugs), and menstrual tampons and pads (regulated as devices), is the in vivo rabbit vaginal irritation (RVI) model (2). There are, however, other types of products for intimate use that must be evaluated for safety, but for which the RVI model is not appropriate. Examples include baby’s nappies, incontinence products and cosmetics (e.g. feminine deodorants and moisturisers, moist toilet tissues, personal lubricants, and bath and body washes).

The efforts of the cosmetic and personal care product industry to replace animal procedures with alternative methods — such as those that use human-derived cells and tissues in vitro, physico-