§ 795.225  Dermal pharmacokinetics of DGBE and DGBA.

(a) Purpose. The purpose of these studies is to determine:

(1) The absorption of diethylene glycol butyl ether (DGBE) after administration by the dermal route.

(2) The biotransformation of DGBE administered dermally.

(3) The dermal absorption of DGBE and diethylene glycol butyl ether acetate (DGBA).

(b) Test procedures—(1) Animal selection—(i) Species. The species utilized for investigating DGBE and DGBA shall be the rat, a species for which historical data on the toxicity and carcinogenicity of many compounds are available and which is used extensively in percutaneous absorption studies.

(ii) Animals. Adult female Sprague Dawley rats shall be used. The rats shall be 7 to 8 weeks old and weigh 180 to 220 grams. Prior to testing, the animals shall be selected at random for each group. Animals showing signs of ill health shall not be used.

(iii) Animal care. (A) The animals should be housed in environmentally controlled rooms with 10 to 15 air changes per hour. The rooms should be maintained at a temperature of 25 ±2 °C and humidity of 50 ±10 percent with a 12-hour light/dark cycle per day. The rats should be isolated for at least 7 days prior to use.

(B) During the acclimatization period, the rats should be housed in cages on hardwood chip bedding. All animals shall be provided with conventional laboratory diets and water ad libitum.

(2) Administration of DGBE and DGBA—(i) Test substances. These studies require the use of 14C-labeled DGBE and DGBA. The use of 14C-DGBE and 14C-DGBA is required for the determinations in paragraphs (a) (1), (2), and (3) of this section because they will facilitate the work and improve the reliability of quantitative determinations.

(ii) Dosage and treatment. (A) Two doses of DGBA shall be used in the study, a “low” dose and a “high” dose. Three doses of DGBE shall be used in the study, a neat “low” dose, an aqueous “low” dose, and neat “high” dose. When administered dermally, the “high” dose level should ideally induce some overt toxicity such as weight loss. The “low” dose level should correspond to a no observed effect level.

(B) For dermal treatment, the doses shall be applied in a volume adequate to deliver the prescribed doses. The backs of the rats should be lightly shaved with an electric clipper shortly before treatment. The dose shall be applied with a micropipette on a specific area (for example, 2 cm²) on the freshly shaven skin.

(iii) Washing efficiency study. Before initiation of the dermal absorption studies described in paragraph (b)(2)(iv)(A) of this section, an initial washing efficiency experiment shall be
performed to assess the extent of removal of the applied DGBE and DGBA by washing with soap and water. Groups of four rats should be lightly anesthetized with sodium pentobarbital. These animals shall then be treated with dermal doses of test substance at the low dose level. Soon after application (5 to 10 minutes) the treated animals shall be washed with soap and water then housed in individual metabolism cages for excreta collection. Urine and feces shall be collected at 8, 24, and 48 hours following dosing. Collection of excreta shall continue every 24 hours if a significant amount of DGBE, DGBA, or metabolites continue to be eliminated.

(iv) Determination of absorption, biotransformation, and excretion. (A) Eight animals shall be dosed once dermally with the low dose of 14C-DGBE.

(B) Eight animals shall be dosed once dermally with the high dose of 14C-DGBE.

(C) Eight animals shall be dosed once dermally with the low dose of 14C-DGBA.

(D) Eight animals shall be dosed once dermally with the high dose of 14C-DGBA.

(E) The high and low doses of 14C-DGBE and 14C-DGBA shall be kept on the skin for 24 hours. After application, the animals shall be placed in metabolism cages for excreta collection. After 24 hours, any test material remaining on the skin will be washed off and the containment cell removed. Radiolabeled material in the wash will be accounted for in the total recovery. Urine and feces shall be collected at 8, 24, 48, 72, and 96 hours after dosing, and if necessary, daily thereafter until at least 90 percent of the dose has been excreted or until 7 days after dosing, whichever occurs first.

(3) Observation of animals—(i) Urinary and fecal excretion. The quantities of total 14C excreted in urine and feces by rats dosed as specified in paragraph (b)(2)(iv) of this section shall be determined at 8, 24, 48, 72 and 96 hours after dosing, and if necessary, daily thereafter until at least 90 percent of the dose has been excreted or until 7 days after dosing (whichever occurs first). Four animals from each group shall be used for this purpose.

(ii) Biotransformation after dermal dosing. Appropriate qualitative and quantitative methods shall be used to assay urine specimens collected from rats dosed with DGBE as specified in paragraph (b)(2)(iv) of this section. Any metabolite which comprises greater than 10 percent of the dose shall be identified.

(c) Data and reporting—(1) Treatment of results. Data shall be summarized in tabular form.

(2) Evaluation of results. All observed results, quantitative or incidental, shall be evaluated by an appropriate statistical method.

(3) Test report. In addition to the reporting requirements as specified in the TSCA Good Laboratory Practice Standards, in part 792, subpart J of this chapter, the following specific information shall be reported:

(i) Species, strain, and supplier of laboratory animals.

(ii) Information on the degree (i.e., specific activity for a radiolabel) and sites of labeling of the test substances.

(iii) A full description of the sensitivity and precision of all procedures used to produce the data.

(iv) Relative percent absorption by the dermal route for rats administered low and high doses of 14C-DGBE and 14C-DGBA.

(v) Quantity of isotope, together with percent recovery of the administered dose, in feces and urine.

(vi) Biotransformation pathways and quantities of DGBE and metabolites in urine collected after administering single high and low dermal doses to rats.

§795.228 Oral/dermal pharmacokinetics.

(a) Purpose. The purposes of these studies are to:

(1) Ascertain whether the pharmacokinetics and metabolism of a chemical substance or mixture (“test substance”) are similar after oral and dermal administration.

(2) Determine bioavailability of a test substance after oral and dermal administration.

(3) Examine the effects of repeated dosing on the pharmacokinetics and metabolism of the test substance.