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Original Article

Subchronic Inhalation Toxicity Study of *n*-pentane in Rats

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Objectives: This study was conducted in order to obtain information concerning the health hazards that may result from a 13 week inhalation exposure of *n*-pentane in Sprague-Dawley rats.
Methods: This study was conducted in accordance with the Organization for Economic Co-operation and Development (OECD) guidelines for the testing of chemicals No. 413 'Subchronic inhalation toxicity: 90-day study (as revised in 2009)'. The rats were divided into 4 groups (10 male and 10 female rats in each group), and were exposed to 0, 340, 1,530, and 6,885 ppm *n*-pentane in each exposure chamber for 6 hour/day, 5 days/week, for 13 weeks. All of the rats were sacrificed at the end of the treatment period. During the test period, clinical signs, mortality, body weights, food consumption, ophthalmoscopy, locomotion activity, urinalysis, hematology, serum biochemistry, gross findings, organ weights, and histopathology were assessed.
Results: During the period of testing, there were no treatment related effects on the clinical findings, body weight, food consumption, ophthalmoscopy, urinalysis, hematology, serum biochemistry, gross findings, relative organ weight, and histopathological findings.
Conclusion: The no-observable-adverse-effect level (NOAEL) of *n*-pentane is evaluated as being more than 6,885 ppm (20.3 mg/L) in both male and female rats. *n*-pentane was not a classified specific target organ toxicity in the globally harmonized classification system (GHS).

Key Words: *n*-Pentane, Subchronic inhalation toxicity, Sprague-Dawley rats, Globally harmonized classification system

Introduction

n-Pentane (CAS No. 109-66-0) is derived from petroleum, such as raw materials, natural gas, and crude oil. *n*-Pentane is a hydrocarbon solvent and a flammable liquid with an estimated production of 100,000-500,000 tons [1]. It is used as a component of aerosol propellant, as a raw material for the production of chlorinated pentanes and pentanols, additive in liquid fumigants, additive in automotive fuels, and as a blowing agent for plastics. Further, it is employed in the production of olefin, hydrogen and ammonia, artificial ice manufacturing, low temperature thermometers, and cosmetics in diverse applications [2].

In Korea, four workplaces with 128 workers produce approximately 584,000 tons of *n*-pentane per year. Additionally, more than 480 workers in 65 workplaces are involved in various manufacturing industries that use approximately 3,710,000 tons of *n*-pentane as the raw material [3].

As a volatile material, *n*-pentane can disperse in ambient conditions and workers can be readily exposed via inhalation at the workplaces. Therefore, the respiratory system serves as the primary target of *n*-pentane exposure.

In human exposure studies, pentane is a central nerve

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system depressant, and can produce chemical pneumonitis or pulmonary edema [4]. In addition, it may cause narcosis, hemorrhage, anorexia, dizziness, depression, confusion, polyneuropathies, seizure, and respiratory arrest [2]. Chronic exposure has resulted in anoxia. Human volunteers, who had an intake of 5,000 ppm pentane vapor for 10 minutes, showed no mucous membrane irritation or other symptoms. The dermal effects of pentane vapor applied to the skin of 5 volunteers were studied. Erythema, hyperemia, swelling, and pigmentation were observed after dermal exposure [5].

There were some *n*-pentane inhalation toxicity tests; yet, all of them are non-good laboratory practice tests and further, exposure concentrations of *n*-pentane were low. The aim of this study was to determine the potential subchronic inhalation toxicity of *n*-pentane via whole-body exposure in Sprague-Dawley (SD) rats. Inhalation exposure to *n*-pentane is the main route for humans because this chemical is volatile and can permeate through the skin. We carried out subchronic toxicity tests with *n*-pentane using SD rats through the Organization for Economic Co-operation and Development (OECD) guidelines in order to provide the exact toxicological information as well as to sort out its globally harmonized classification system (GHS) category.

Materials and Methods

Animals

Eighty 6-week-old SD rats (40 males and 40 females) were obtained from a specific pathogen-free colony from the Central Lab Animal Inc. (Seoul, Korea); the rats were used after 6 days of quarantine and acclimatization. The animals were housed in a room maintained at a temperature of 22 ± 3°C and a relative humidity of 50 ± 20% with artificial lighting from 08:00 to 20:00 along with 12-15 air changes per hour. The animals were housed individually in wire-bottomed stainless steel wire mesh cages that were placed in exposure chambers. They were allowed sterilized tap water and commercial rodent chow (5053-PICOLAB RODENT 20; PMI Nutrition, St. Louis, MO, USA) *ad libitum*. Before rats were obtained for research, the rat studies were approved by an Animal Ethics Committee (IACUC-11-3) in order to ensure appropriate animal care.

Test chemical and exposure

n-Pentane was purchased from Sigma-Aldrich (Lot No. 83396PM; St. Louis, MO, USA). Whole-body exposure chambers (Shibata Co., Niigata, Japan), including a gas generator (Shibata Co.), were used to expose rats to *n*-pentane. The test animals were exposed to 340, 1,530, or 6,885 ppm *n*-pentane or fresh air for 6 hours per day, 5 days per week, for 13 weeks. The inhalation exposure was carried out from 10:00 to 16:00 in a stainless steel chamber (1,000 L). The experimental design was based on the usual working schedule for workers as well as on the major exposure route for the test chemical.

Experimental design

Prior to testing, rats were evaluated by clinical observations and body weight determinations over a course of a 6 day quarantine period in order to assure freedom from potential confounding variables. Forty males and 40 females were randomly assigned to four experimental groups: three treatment groups receiving 340, 1,530, and 6,885 ppm *n*-pentane, and a vehicle control group. Each group consisted of 20 rats (10 males and 10 females). All of the rats were sacrificed after treatment for 13 weeks. The experimental concentrations were selected based on the results of an acute inhalation toxicity study. Considering the classification and safety of GHS, we selected 340 ppm as a low dose. One thousand five hundred thirty and 6,885 ppm were selected as the medium and high dose, respectively, using a scaling factor of 4.5.

Temperature, relative humidity, pressure, and air ventilation in the chambers were recorded using an environmental controller (Shibata Co.). The temperature and relative humidity were maintained at 23.6-25.4°C and 45.4-53.9%, respectively. The concentrations of *n*-pentane in the chambers were calibrated with a standard gas (RIGAS, Daejeon, Korea). The conditions used for detecting *n*-pentane by gas chromatography (Shimadzu Co., Kyoto, Japan) were as follows: detector temperature, 120°C; oven temperature, 100°C; injector temperature, 120°C; and injection volume, 1 mL of gas sample. *n*-Pentane vapor concentrations in the chambers were measured every 15 minutes during exposure and were controlled to be within ± 5% of the target concentration using a computer. The mean concentration, which was measured every 30 minutes for 6 hours, was taken as the value on a given day. This was then averaged over the 13-week exposure period in order to obtain the mean and standard deviations; the daily gas concentrations in the three chambers were measured at 339.8 ± 4.52, 1,540.6 ± 25.66, and 6,917 ± 91.64 ppm, respectively.

Clinical examination

All animals were observed twice daily (before and after exposure) throughout the study period for any clinical signs of toxicity, morbidity, and mortality.

Body weights of each rat were measured at the beginning of exposure and once a week during the exposure period. Food consumption was measured at the beginning of exposure