American Chemistry Council
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January 23, 2003

9355 '03 JAN 23 P3:33

Dockets Management Branch
Division of Management Systems and Policy
Office of Human Resources and Management Services
Food and Drug Administration
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, MD 20852

Re: Docket No. 02D-0325: Medical Devices Made with Polyvinylchloride (PVC) Using the Plasticizer di-(2-Ethylhexyl)phthalate (DEHP); Draft Guidance for Industry and FDA

Supplement to December 4, 2002 comments

Dear Madam or Sir:

On December 4, 2002, the Phthalate Esters Panel of the American Chemistry Council submitted comments in response to the above-referenced draft guidance document released by FDA's Center for Devices and Radiological Health (CDRH) Office of Device Evaluation. In those comments, the Panel provided preliminary results for a study of marmosets that was recently completed in Japan, and stated it would provide further information to CDRH as it became available.

The abstract for this study, which will be presented at the March 2003 Annual Meeting of the Society of Toxicology (SOT), is now posted on the SOT site.[1] A copy of the abstract is provided as Attachment 1. It states that, at doses up to 2500 mg/kg/day, administered from weaning to sexual maturation (a sensitive period for testicular toxicity in rats), there was no evidence of testicular effects. The examination included electronmicroscopy. This study provides strong additional evidence that primates are much less sensitive to testicular effects than are rodents, and that CDRH's tolerable intake based on rat data is very conservative.[2]

The Panel will continue to provide information on this study as it becomes available. If you have any questions, please call me at 703-741-5623 or email me at Marian_Stanley@americanchemistry.com.

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[1] Y. Tomonari; Y. Kurata; T. Kawasuso; R. David; G. Gans; M. Tsuchitani; M. Katoh (2003). Testicular Toxicity Study of Di(2-Ethylhexyl)Phthalate (DEHP) in Juvenile Common Marmoset. Society of Toxicology 42nd Annual Meeting, March 13, ID No. 1866. Available at http://www.toxicology.org/MemberServices/Meetings/am2003/index.html (click on "Itinerary Planner" under "Scientific Programs," click on "Open/create itinerary," register to create an itinerary, click on Thursday, March 13, click on the 8:30 Poster Session: Safety Evaluation II, scroll down to the title and click on "view abstract.")

[2] *See also* the discussion of primate data in Attachment A to the Panel's Dec. 4, 2002 comments.

The Panel will continue to provide information on this study as it becomes available. If you have any questions, please call me at 703-741-5623 or email me at Marian_Stanley@americanchemistry.com.

Sincerely,

Marian K. Stanley

Marian K. Stanley
Senior Director, CHEMSTAR
Manager, Phthalate Esters Panel

cc: Daniel G. Schultz, M.D.
Director
Office of Device Evaluation

Philip J. Phillips
Deputy Director for Science and Regulatory Policy
Office of Device Evaluation

Ann Hawthorne
Guidance Development Officer
Office of Device Evaluation

Attachment 1

Society of Toxicology 42nd Annual Meeting

ID# 1866
Location: South Foyer Lobby
Time of Presentation: Mar 13 8:30 AM - 8:30 AM
Category (Subcategory): Safety Evaluation, (Reproductive System)

TESTICULAR TOXICITY STUDY OF DI(2-ETHYLHEXYL)PHTHALATE (DEHP) IN JUVENILE COMMON MARMOSET.

Y. Tomonari[1]; Y. Kurata[1]; T. Kawasuso[1]; R. David[2]; G. Gans[3]; M. Tsuchitani[1]; M. Katoh[1]
1. Kashima Laboratory, Mitsubishi Chemical Safety Institute Ltd., Kashima, Ibaraki, JP;
2. Consultant to Eastman Chemical Company, Rochester, NY, USA;
3. BASF AG, Ludwingshafen, , DE;

Rats exposed to DEHP during the pre- and peri-adolescent period have been shown to be sensitive to testicular effects, hence this study was conducted to characterize the potential effects of DEHP on the reproductive organs in the juvenile primate. Male marmosets aged 3 months (5-6/group) were treated orally with 0 (corn oil), 100, 500, and 2500 mg/kg DEHP once per day for 15 months until sexual maturity. The reproductive organs (testis, epididymis, prostate, seminal vesicle), pituitary, thyroid, pancreas, liver, adrenal, kidney, and spleen were weighed and were examined microscopically. Testicular 3-beta hydroxysteroid dehydrogenase(3-beta HD) activity was determined histochemically. The testis was also subjected to electronmicroscopic examination and to a determination of mRNA expression of PPAR-alpha (peroxisome proliferator-activated receptor). Mean body weights of each DEHP-treated group were comparable to that of the control group. There were no differences in the mean organ weights in each DEHP-treated group. One male in each DEHP-treated group showed low values in testis, epididymis, prostate, and seminal vesicle weights corresponding to the low body weights. The animals exhibiting low testis, epididymis, prostate, and siminal vesicle weights had reterded growth in general. No treatment-related findings were observed microscopically in any organs except for above changes. No remarkable changes were observed electronmicroscopically in the testis. There were no differences in a 3-beta HD activity or mRNA expression of PPAR-alpha between animals in the control group and those in the each DEHP-treated group. In conclusion, exposure of juvenile marmosets (primates) to high dose levels of DEHP prior to and during adolescence (a sensitive period for testicular toxicity in rats) showed no evidence of testicular effects.