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U. S. Environmental Protection Agency
Attention: 8(e) Coordinator
Document Control Officer
Office of Pollution Prevention & Toxic Substances, 7407
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Ladies and Gentlemen:

Subject: Notice in Accordance with TSCA Section 8(e) – Abstracted study results of a developmental toxicity study in rats with N-methyl-2-pyrrolidone.

BASF Corporation has become aware of results of a developmental toxicity study in rats with N -methyl-2-pyrrolidone (CAS 872-50-4). The findings of this study were absracted in the proceedings of the 29th Conference of the European Teratology Society, Balatonfured – Hungary, 2001. The absract for the study and a portion of the Scientific Program are attached.

Though BASF Corporation neither sponsored nor conducted this study, BASF Corporation understands that the reporting of the absracted study results is in accordance with EPA's policy. Any additional reports or information that we receive regarding these absracted study resuts will be forwarded to the Agency and Material Safety Data Sheets will be updated with this information as required.

Very truly yours,

BASF CORPORATION

Edward J. Kerfoot

Edward J. Kerfoot, Ph.D.
Director, Toxicology and Product Regulations

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Enc.

8EHQ-02-15084

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BALATONFÜRED - HUNGARY, 2001

29th CONFERENCE OF THE
EUROPEAN TERATOLOGY SOCIETY

FINAL PROGRAM

2-5 SEPTEMBER, 2001

EUROPEAN TERATOLOGY SOCIETY

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SCIENTIFIC PROGRAM

Sunday, 2nd September

10.00 - 22.00 **Registration**
12.00 - 14.00 **Lunch for EC participants and Council members**
14.00 - 18.00 **Education Course**
Place: Lecture room 4.

Hermann B. W. M. Kočter, OECD
General Introduction to OECD Test Guideline Development:
- The process of guideline development;
- The content and purpose of the Standard Project Submission Form (SPSF);
- Expert involvement;
- Solna Meeting on validation and follow-up;
- Testing strategies;
- Endocrine disrupters test development and validation

Horst Spielmann, Germany
Validation of New and Revised Test Methods:
- How much flexibility?
- One-approach-fits-all or tailor-made designs?
- The importance of a prediction model;
- Is there a difference between the validation of animal tests and of *in vitro* tests?

16.30 - 16.45 **Coffee Break**

Ulla Haas, Denmark
Case Story: Development of Test Guideline 426: Developmental Neutrotoxicity:
- The start (Expert Consultations on Neutrotoxicity and Development Toxicity);
- The Groundwork: EPA Guidelines;
- The Co-operation: Denmark and USA;
- The comments on the first proposal and;
- The Consultation Meeting, jointly with ILSI in Washington October 2000.

Horst Spielmann, Germany; Andrea Seiler, Germany; Aldert Piersma, The Netherlands
Validation of in vitro tests for embryotoxicity
- Results of the ECVAM validation study
- Embryonic stem cell test (EST)
- Whole embryo culture test and micromass test

19.30 - 20.30 **Welcome Reception**

Monday, 3rd September

08.00 - 18.00 **Registration**
08.45 - 09.00 **Opening Address**
Place: Lecture room 1.

BLASTOMERE BIOPSY AS THE FIRST STEP IN PREIMPLANTATION DIAGNOSIS

Fancsovits P*., Bán Z., Tóthné G.Zs., Urbancsek J., Papp Z., First Department of Obstetrics and Gynaecology, Semmelweis University Medical School, Budapest

Preimplantation genetic diagnosis (PGD) allows the detection of genetic defects in embryos following in vitro fertilization. Subsequent transfer of unaffected embryos can lead to the establishment of a normal pregnancy with healthy offspring. PGD offers invaluable help for couples at high risk of having children with inherited disease. The aim of our study was to introduce the method of blastomere biopsy in a preliminary study.
For blastomere biopsy we used supernumerary IVF embryos which were not appropriate for transfer. Embryos were biopsied with an electrically and hydraulically controlled micromanipulator. Biopsies were performed 3 days after fertilization, at 6-10 cell stage. Zona pellucida was opened by chemical method, using acidified Tyrode's solution. From each embryo 1-3 blastomeres were aspirated for further genetic analysis.
Those embryos which seemed to be able to develop further after biopsy were kept in culture in order to determine post-biopsy survival rates.
104 blastomeres of 35 embryos were removed. Post-biopsy development rates were examined in 14 embryos. 9 (64%) showed cell division after biopsy and 6 (43%) reached the morula or blastocyst stage during in vitro culture.
These preliminary results and the first experiences obtained in this study indicate that preimplantation genetic diagnosis could be introduced in our future clinical practice.

DEVELOPMENTAL TOXICITY OF N-METHYL-2-PYRROLIDONE ADMINISTERED BY GAVAGE OR INHALATION TO RATS

A.M. Saillenfait, F. Gallissot, I. Langonné, J.P. Sabaté*, G. Morel. Department of Pollutants and Health, National Institute of Research and Safety, 54501 Vandoeuvre, France

N-methyl-2-pyrrolidone (CAS 872-50-4, NMP) is an industrial solvent used extensively in chemical processing.
In this study, pregnant Sprague-Dawley rats (25-27/group) were administered NMP from Day 6 to 20 of gestation by inhalation (0, 30, 60, or 120 ppm, 6 hours per day) or by gavage (0, 125, 250, 500, or 750 mg/kg/Day). Ceasarian sections were performed on Day 21 of gestation and the live fetuses were submitted to external examination.
Following inhalation exposure, maternal toxicity evidenced by significant decreases in body weight gain occurred at 60 and 120 ppm. Decreased food consumption was also observed at 120 ppm. Embryonic survival and external morphology of live fetuses were not affected at any concentration. Developmental toxicity was indicated by decreases in fetal body weights at 120 ppm as compared to controls (air).
Following oral administration, maternal toxicity manifested by reduced body weight gain and food consumption was observed at 500 and 750 mg/kg. Adverse effects on the embryo/fetal development were apparent at 250 mg/kg and above. A high incidence of post-implantation loss was observed at 750 mg/kg (94 %). There was a dose-related decrease in fetal weights, which were statistically different from vehicle control (distilled water) at doses 250mg/kg. Characteristic malformations were also observed. At 250 mg/kg, one fetus exhibited anal atresia and absence of tail. At 500 mg/kg, eleven fetuses from nine different litters showed malformations including anasarca and/or anal atresia and absence of tail. At 750mg/kg, there were one case of proboscis and one case of anasarca (267/21, 276/21, 304/24, 311/25, and 19/8 fetuses/litters examined at 0, 125, 250, 500, and 750 mg/kg, respectively). These external malformations were considered as indicative of teratogenic effects of ingested NMP.

CHROMOSOMAL STUDY ON CONGENITAL CENTRAL NERVOUS SYSTEM ANOMALIES

Tetsuji Kadotani*[1], Tomiko Kadotani*[1] and Toshihide Saito[2], [1] The Kadotani Medical Research Foundation, Higashi-Hiroshima, Japan. [2] Hiroshima Prefectural Rehabilitation Center for the Disabled, Higashi-Hiroshima, Japan.

Chromosomal study was conducted on 81 cases of congenital central nervous system anomalies to explore the causes of these anomalies. These included 24 cases of neural tube defect (21 spina bifida and 3 cranioschisis), 17 of cortical dysplasia (Lissencephaly, schizencephaly and heterotopia), 17 of microcephalus, 10 of hydrocephalus, and 13 of others. They were investigated on chromosomal abnormalities and fragile sites. Eight cases out of the 81 had chromosomal abnormlalities showing high incidence of 9.9%. Three cases out of the 8 had the abnormalities transmitted from their parents (3.7%). The frequency of the cases having chromosomal abnormalities in each group was 2 per 24 cases in neural tube defect: the incidence being 8.3%, 0 per 17 cases in cortical dysplasia: the incidence being 0%, 4 per 17 cases in microcephalus: the incidence being 23.5%, 0 per 10 cases in hydrocephalus: the incidence being 0%, 2 per 13 cases in other congenital central nervous anomalies: the incidence being 15.4%. The highest incidence of chromosomal abnormalities was shown in microcephalus (23.5%). Seven cases showed normal variations and 66 cases showed
normal karyotypes. Chromosome fragile sites were studies on 71 cases and found in 45 cases, being 63% in incidence. They were all common fragile sites.

STUDIES ON THE TERATOGENIC EFFECTS OF LAMOTRIGINE (LT) IN MOUSE FETUSES

***Bastaki, SMA, R. Padmanabhan, Y.M., Abdulrazzaq, S.I. Chandranath and M. Shafiulla,** Faculty of Medicine, UAE University, Al Ain, United Arab Emriates.

One of the major complications of antiepileptic drug (AED) therapy during pregnancy is an increased incidence of congenital malformations in the offspring (see for references Padmanabhan et al., Cong Anom 2000:259-268). The calculated risk of malformations in the fetuses exposed to AED is 7-10%. Most of the AED tested so far have been found to be teratogenic in human and experimental studies. Lamotrigine (LT) is a relatively recently introduced AED. Its teratogenic properties have not been reported in the literature. We administered (ip) single dose [50 300 mg/kg of LT (Lamictal, Wellcome Co, UK)] or three doses (25 75 mg/kg) to groups of TO mice starting at 9 am on gestation day (GD) 7 or 8. Fetuses were collected on GD 18. The maternal amino acid profile was determined by HPLC. There was a significant reduction in food and water consumption and body weight gain of the LT treated animals. Maternal mortality was dose-dependent. Except in the 25 mg/kg group, all treated animals exhibited clonic type of seizures starting within 5 minutes and lasting several hours. A consistent reduction in body weight, and dose-dependent increase in craniofacial malformations (exencephaly, cleft palate, arched palate, midfacial hypoplasia etc.), caudal regression and skeletal defects occurred in the high single dose groups and in the triple dose groups. Treated animals also exhibited alterations in plasma amino acid concentrations such as methionine and of dopamine. These data indicate that maternal toxicity might contribute significantly to fetal malformations in LT treated mice. (Supported by UAE University)