EUROPEAN CENTRE FOR ECOTOXICOLOGY AND TOXICOLOGY OF CHEMICALS AISBL

To: Recipients of JACC 42

HV/mls/JACC 42 corrigendum

Brussels, 15 December 2004

Dear Sir or Madam,

Corrigenda to JACC No. 42 - Tetrafluoroethylene (CAS No. 116-14-3)

Following publication of the above report, some unfortunate errors occurred in the carcinogenicity assessment, which necessitate modification of the published text. Would you therefore kindly replace the existing pages 1, 2, 4 and 45/46 with the five new pages provided.

The changes affect:

- the Executive summary on page 1, paragraph 5;
- the Summary and conclusions on page 4, paragraph 5;
- Section 8.5.3 Evaluation on pages 45 and 46, paragraphs 2-5.

Please advise if you have any difficulties.

With our sincere apologies for the oversight and inconvenience,

Yours faithfully,

Dr Michael Y. Gribble
Secretary General

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EXECUTIVE SUMMARY

This report has been produced as part of the ECETOC Joint Assessment of Commodity Chemicals (JACC) programme. It presents a critical evaluation of the toxicity and ecotoxicity data on tetrafluoroethylene (TFE) that could inform the hazard/risk assessment required under current OECD/EU schemes [a,b]. In the USA, TFE is included in the EPA Chemical Right-to-Know Initiative [c].

TFE is a colourless gas that is mainly used in the production of polytetrafluoroethylene and other fluorinated polymers. It is sparingly soluble in water. Any TFE released into the environment will be distributed to the atmosphere, where it will quickly degrade to carbon dioxide and hydrogen fluoride that is washed out by rain. TFE does not contribute directly to the greenhouse effect (global warming) and has no effect on the stratospheric ozone layer, but may enhance the formation of tropospheric ozone, more or less significantly, depending on the quantities emitted.

In the aquatic environment, no hydrolysis of TFE will occur and it is not prone to rapid biodegradation and bioaccumulation. TFE will not adsorb significantly to soils and sediments. Although experimental data are not available, model calculations predict that that TFE is not toxic to environmental organisms.

Short-term inhalation exposure of laboratory animals to high doses of TFE did not evoke cardiac sensitisation or anaesthetic effects that are typically found with other fluorinated compounds. With TFE, the primary effect was damage to the kidney, though overall the toxcity was judged to be low. Longer-term exposures also resulted in a low level of toxicity manifest as kidney effects and anaemia in rats and mice, and possibly testicular changes in hamsters. No specific study of the reproductive effects of TFE is available.

TFE is not genotoxic either *in vitro* or *in vivo*. The principal metabolite of TFE, S-1,1,2,2-tetrafluoro-ethyl-L-cysteine, is also not mutagenic *in vitro*. In long-term carcinogenicity studies in rats and mice, exposure to high concentrations of TFE vapours produced haemangiosarcomas and hepatocellular tumours in the liver (mice and rats), probably due to metabolites formed via recently identified pathways, and of tubular cell tumours in the kidney (rats only). In mice, there was also an excess of histiocytic sarcomas in some organs. Differences in the rate of metabolism of TFE in vitro suggest that the risk to humans of developing tumours is significantly less than in rats or mice. The current lack of knowledge about the mechanisms involved in the development of these three tumour types precludes a full evaluation of the hazard to humans from exposure to TFE.

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[a] OECD Existing Chemicals Programme [http://www1.oecd.org/ehs/hazard.htm]

[b] EU Existing Chemicals Work Area [http://ecb.ei.jrc.it/existing-chemicals]

[c] US-EPA high production volume (HPV) challenge list [http://www.epa.gov/oppt/chemrtk/]

THE ECETOC SCHEME FOR THE JOINT ASSESSMENT OF COMMODITY CHEMICALS

This report has been produced as part of the ECETOC programme for preparing critical reviews of the toxicology and ecotoxicology of selected existing industrial chemicals. In the programme, commodity chemicals (i.e. those produced in large tonnage by several companies and having widespread and multiple uses) are jointly reviewed by experts from a number of companies with knowledge of the chemical. It should be noted that in a JACC review only the chemical itself is considered; products in which it appears as an impurity are not normally taken into account.

This document presents a critical evaluation of the available toxicology and ecotoxicology of tetrafluoroethylene (CAS No. 116-14-3).

Where relevant, the Task Force has graded the (eco)toxicological studies by means of a "code of reliability" (CoR) to reflect the degree of confidence that can be placed on the reported results. The codes and criteria used to assess reliability are included in Appendix A.

In the rat, effects were seen at the lowest dose of 312 ppm (1,275 mg/m^3) (lowest-observed-effect level, LOEL). In addition, both species showed secondary hypoproliferative anaemia when exposed to TFE. Testicular atrophy was not seen in rats and mice. In hamsters, no evidence of kidney toxicity or anaemia was seen, but signs of testicular atrophy were found after 13 weeks of exposure to 600 ppm (2,450 mg/m^3) and above. The NOAEL for these effects was 200 ppm TFE (820 mg/m^3).

No signs of respiratory tract irritation were seen in the acute or repeated-dose animal studies.

TFE has been fully assessed for its genotoxic potential in a number of studies. It did not induce gene mutations in bacteria and mammalian cells *in vitro*, and was not clastogenic in Chinese hamster ovary (CHO) cells *in vitro* or in two micronucleus tests in mice. Hepatocytes isolated from mice exposed to TFE showed no evidence of unscheduled DNA synthesis (UDS). Therefore, TFE is not genotoxic both *in vitro* and *in vivo*. In mice exposed to TFE for 2 years, TFE induced hepatocellular neoplasms developed by pathways independent of ras mutations. A cysteine conjugate of TFE, S-1,1,2,2-tetrafluoroethyl-L-cysteine, a nephrotoxic metabolite activated by renal C-S lyases (β-lyases), is also without mutagenic activity.

TFE was found to be carcinogenic in rats and mice exposed by inhalation. Mice exposed to concentrations of 312, 625 or 1,250 ppm TFE (1,275, 2,555 or 5,110 mg/m^3) for 95 weeks showed a concentration-related increased incidence of liver tumours (hepatocellular adenoma and/or carcinoma and haemangiosarcoma) in both sexes, the effects in all exposed groups (except males exposed to 156 ppm; 638 mg/m^3) being statistically significantly different to controls. Increased incidences of histiocytic sarcoma were also observed in a number of organs.

In the rat, the kidney was the primary target organ. Male rats were exposed to 156, 312 or 625 ppm TFE (638, 1,275 or 2,555 mg/m^3) for 103 weeks and increased mortality occurred in those exposed to the highest concentration. Female rats were exposed to 312, 625 or 1,250 ppm TFE and increased mortality was seen in all exposed groups. In addition, absolute and relative liver weights were increased in both sexes. Exposure to TFE caused an increase in the incidence of renal tubular adenoma and adenocarcinoma, and combined adenoma-carcinoma in both sexes; there was also an increased incidence of haemangiosarcoma in the liver of female rats exposed to 625 ppm of TFE.

TFE is metabolised by glutathione conjugation and via the mercapturic acid pathway. The cysteine conjugate of TFE is also known to be a substrate for renal C-S lyase. Studies on the mode of action of TFE as a rodent carcinogen suggest that the hepatic and renal carcinogenicity of TFE in rodents is associated with its metabolism via the glutathione and C-S lyase pathways. In rats and mice, the highest C-S lyase activities are found in the target organs, the rat kidney and mouse liver.

Mononuclear cell leukaemia

Increased incidences of mononuclear cell leukaemia were observed in some of the exposed groups, particularly in females where the increased incidences were statistically significantly different from controls, although the effect was not dose-related in either sex (Table 11). The incidence in the control males (68%) was outside the historical control range for the conducting laboratory (38 - 66%), as were the incidences observed in males exposed to 156 (86%) and 312 ppm (76%). In females, the incidences in rats exposed to 312 (62%) and 1,250 (72%), but not 625 (46%) ppm TFE, were also outside the range of historical controls.

8.5.3 Evaluation

TFE causes toxic effects in various organs and is carcinogenic in both the rat and the mouse after lifetime exposure.

The survival rates of all groups of mice exposed to TFE were reduced compared to controls, although there were no significant reductions in the mean body weights of survivors at the end of the study. In the liver, multifocal coagulative necrosis was observed in all groups of exposed males, whilst haematopoietic cell proliferation was observed in all groups of exposed females. Angiectasis was also observed in all groups of exposed males and females. In addition, increased incidences of renal tubular dilatation and karyomegaly, principally in the inner cortex, were also observed in all groups of exposed males. Karyomegaly was the only renal finding in females when exposed to 1,250 ppm TFE (5,110 mg/m^3). No NOAEL can be established in the mouse on the basis of the information currently available.

Exposure of mice to TFE caused increased incidences of haemangiosarcoma of the liver and histiocytic sarcoma (all organs) in all groups of exposed males and females at the end of the study. Increased incidences of haemangiosarcoma were also apparent in groups of both males and females exposed to the highest concentrations of TFE for 15 months. Increased incidences of hepatocellular tumours were also observed in all exposed groups of males and females.

In the rat, TFE caused increased mortality following exposure to 625 ppm TFE (2,555 mg/m^3) and in all groups of females (up to 1,250 ppm; 5,110 mg/m^3) when exposed for their lifetime. The primary target organs for toxicity in the rat were the kidney and the liver. Increased absolute and relative kidney weights and excesses of renal tubular adenoma or adenoma and carcinoma combined were seen in all exposed groups except males exposed to 156 ppm TFE (638 mg/m^3). In addition, increases in absolute and relative liver weight were observed in some groups of exposed females, along with increased incidences of clear cell and mixed cell foci and hepatic angiectasis in all exposed groups of males and some exposed groups of females. TFE caused an increase in the

incidence of hepatocellular adenoma and/or carcinoma combined in males exposed to 312 ppm TFE (1,275 mg/m^3) and all exposed groups of females, along with an increased incidence of haemangiosarcoma in the of females exposed to the highest concentration of TFE.

No NOAEL for the liver effects could be determined in the male or female rat or for renal effects in male rats following life-time exposure to TFE. A concentration of 156 ppm (638 mg/m^3) was a NOAEL for renal tumours in the male rat and 312 ppm (1,275 mg/m^3) was a NOAEL for all renal effects in the female rat.

8.6 Reproductive and developmental toxicity

No specific toxicity studies are available for reproductive and developmental toxicity.

Rat and mouse

In the 13-wk repeated-dose toxicity studies in F344 rats and B6C3F$_1$ mice exposed to TFE for 13 weeks (for details see Section 8.3), there were no treatment-related differences in epididymal spermatozoa or vaginal cytology parameters between control and exposed groups of rats or mice (NTP, 1997)

Hamster

Groups of 10 male Lak:LVG (Syrian) hamsters were exposed (6 h/d, 5 d/wk) for 14 days to TFE at concentrations of 0, 101, 500, 991 or 2,489 ppm TFE (0, 413, 2,040, 4,050, 10,180 mg/m^3) (Nash *et al*, 1981). Half of the animals from each group were killed immediately after the tenth exposure; the others were maintained for a 14-d recovery period. No clinical signs of toxicity were seen. There were no significant changes in organ weights. There was evidence of testicular atrophy in hamsters exposed to 2,489 ppm TFE (10,180 mg/m^3) after the 14-d recovery period, but not in those sacrificed after the tenth exposure.

Groups of 15 male and 15 female Lak:LVG (Syrian) hamster were exposed (6 h/d, 5 d/wk) to 0, 203, 605 or 1,989 ppm TFE (0, 830, 2,473 or 8,130) for 13 weeks (Schneider *et al*, 1982). No TFE-related effects were observed in the females. Male hamsters exposed to either 605 or 1,989 ppm TFE exhibited a variable incidence of testicular immaturity. In addition, a TFE-induced focal hypocellularity of the germinal epithelium of seminiferous tubules was observed in those exposed to 1,989 ppm TFE. The atrophic testicular changes were noted in hamsters that had either mature or immature testes. Because of the nature of the lesion and the confounding effect presented by delayed testicular maturation, it could not be determined with certainty whether or not a TFE-related effect had occurred in hamsters exposed to 605 ppm TFE. As no such effects were seen in hamsters exposed to 203 ppm TFE, this dose was a clear NOAEL for the effect on the testes.