We support that classification of Bisphenol A for reproductive effects has to be reconsidered, since numerous studies have been produced in the recent years.
Under this respect, we consider that the studies performed by sub-cutaneous administration or other parenteral routes (intramuscular, i.p.) may serve as proof-of-principle, i.e., to show the potential of bishenol A to act as a reproductive toxicant and the main targets of its reproductive effects. However, for classification and labelling purposes, priority has to be given to studies using treatment routes relevant to consumer's exposure, such as oral, diet, drinking water, inhalation.
We support the classification proposal as **1b** for reproductive toxicity (R60), based on the consistent observation of reproductive impairment at oral/dietary dose levels. Considering only studies performed after 2000 using oral (gavage, diet. drinking water) routes:

Female reproduction
- increased ovarian meiotic abnormalities upon prepubertal exposure in mice (Hunt et al., 2003)
- increased resorption rate in mice exposed since mating (Al-Hiyasat et al., 2004)
- dose-related delayed puberty (two-generation study in rats; Tyl et al., 2002)
- endometrial proliferation (increased thickness of uterine epithelia and stroma, less apoptotic cells) with reduced ER-α expression in rats exposed to 1.2 mg/kg bw in utero and during lactation (Mendoza-Rodriguez et al., 2011); at much higher in utero exposure (50 mg/kg) the thickness of the uterine epithelium is reduced with altered expression of estrogen receptors (Schönfelder et al., 2004)
- irregular estrous cycle upon developmental (pre- and neonatal) exposure (Rubin et al., 2001; Mendoza-Rodriguez et al., 2011)

Male reproduction
- Impaired spermatogenesis upon in utero exposure in rats (Tinwell et al., 2002; Iida et al., 2002) also with demonstrated impaired reproductive ability (Salian et al., 2009)
- Reduced testis and seminal vesicles weight, with reduced Leydig cells testosterone production in rats exposed in utero and neonatally (Akingbemi et al., 2004)
- Reduced testosterone (Akingbemi et al., 2004; Della Seta et al., 2006) and LH (Akingbemi et al., 2004) serum levels in rat exposed during prepubertal phase (Akingbemi et al., 2004); reduced reproductive performance also observed (Della Seta et al., 2006)
- Delayed puberty in rats exposed in the prepubertal phase (Tan et al., 2003)
- Impaired spermatogenesisis with reduced testis and epidydimal weight and increased prostate weight in adult rats (Chitra et al., 2003)

Apparently the above effects were observed in the absence of other toxic effects that may cause reproductive impairment as a secondary consequence. Thus, the overall picture of BPA effects on fertility/reproductive function fulfills the criteria for classification as **1b.**
The data available hint to some further observations:
- The effects of BPA are more complex than being simply “estrogenic” and hint to modes of action modulated by dose, sex and lifestage; species- and strain-related susceptibility have been observed, mice appearing as less susceptible. This interplay among factors modulating BPA effects may partly explain why some studies contradict the majority of findings as no effects are shown; this aspect is surely worth investigating for a refined risk assessment. However, the overall the overall weight of evidence points to clearly point to an impaired reproductive function in both sexes, encompassing secveral endocrine, morphological and functional parameters and with enhanced sensitive of the prenatal and also prepubertal stages. Thus, for classification purposes BPA should be considered as a chemical capable to elicit clear-cut reproductive effects in both sexes through relevant exposure routes.
- Reproductive effects were apparently less evident in the two-generation studies, however these were not entirely absent as shown by the dose-related delayed puberty seen also at the intermediate dose in the rat two-generation study by (Tyl et al., 2002). This is another finding definitely worth investigating: data may suggest that the repeated pulse exposure related to gavage is much more effective than continuous low-level exposure elicited by the long term dietary administration.

One might speculate that the aggregate, multiple way exposure of humans is more similar to the

repeated pulse scenario, whereas a continuous dietary exposure might be more relevant to cumulative chemicals.
Again, this issue is definitely worth investigating for risk assessment, but it bears little weight for classification purposes, that currently rely on rather stringent, hazard-based criteria

Moreover, consideration should be given to available human data:

- Biomonitoring data in humans indicate a continuous aggregate exposure, with a prolonged presence of detectable internal levels
- Humans may have more efficient detoxification mechanisms than rodents; however, many differences exist within the human population, related to genetics, sex and lifestage
- Epidemiological investigations suggest a relationship between BPA levels and increased risk of reproductive disorders in women (infertility, recurrent miscarriage, impaired IVF), while in males correlations with impaired spermatogenesis and altered endocrine balance (steroid hormones, FSH, Inhibin B) have been observed.

Overall human data are not robust enough to support a 1a classification; however, these studies support the evidence provided by the animal studies pointing out that bisphenol A should be classified as 1b for reproductive toxicity.