# Isoproturon

## Position on Classification for Reproductive Toxicity

### Expert Statement

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## Introduction

Isoproturon is a herbicidal active ingredient regulated under Reg. (EC) 1107/2009. Two separate entities apply for re-inclusion into Annex I in Europe: the Isoproturon Task Force under lead of Bayer CropScience, and Adama.

Isoproturon is harmonized classified in Reg. 1272/2008 as Carc Cat. 2 (H351), Aquatic Acute 1 (H 400) and Aquatic Chronic 1 (H 410).

Germany is rapporteur member state (RMS) for the re-inclusion process. Germany has submitted a CLH-report to ECHA. This report proposes to add classifications with Repro Cat. 2 (H361f) and STOT RE 2 (H373 (blood)) to the existing classification and to re-discuss the M-factor for the environment. This classification, if confirmed by ECHA, would trigger the cut-off criteria for endocrine disruption and effectively ban Isoproturon from the EU market. No new information is available on reproductive toxicity since the current harmonized classification was set.

## Position of Adama

Adama disagrees with a classification for Repro Cat. 2. The classification proposal is based on “”some evidence” for adverse effects on reproduction“ (citation from the public RAR, Vol. 1, page 54, and the CLH report, page 51), namely “reproduction toxicity seen in rats is due to reduced male fertility”.

No new information on reproductive toxicity that was not already available for setting the current harmonized classification was generated. A reliable two-generation study in rats is available (Becker et al., 1989). The only finding in this study was a small reduction in number of implantation sites at 2000 ppm, a dose level that was above the maximum tolerated dose (defined as >10% on body weight development) in all generations investigated. Also, comparing the dose to toxicity seen in repeated dose studies at 2000 ppm, it is clear that the MTD was significantly exceeded, as liver damage at this dose level was significant (leakage markers in blood as evidence of liver cell destruction) and hemolytic anemia is present. This finding is not suitable as a basis for classification. This clinical picture of toxicity is excessive, and not compatible with a successful reproductive performance.

All evidence for “reduced male fertility” is based on 3 multigeneration studies (from the same laboratory and same study director conducted in a close period of time) and one publication generated in India in the 1990s. The earlier mentioned two-generation study (Becker et al. 1989) found no effects on male fertility, despite dosing more than 4-fold higher. All those studies were previously evaluated by the RMS (Germany). Based on this evaluation, the effect “reduced male fertility” was not deemed to trigger a reproductive toxicity classification.

Adama had access to one of the multigeneration reports (Bhide 1990, TOX95-50738). A independent consultant to Adama could get access to and analyse a second report (Becker et al., 1989) and the publication (Sarkar et al., 1997). In-depth expert analysis of these three contributions revealed that the Becker study is reliable with restrictions (as expected considering the age of the study), while very significant methodological deficiencies were identified in both the two-generation study by Bhide and the publication by Sakar. These include underfeeding of the experimental animals with inappropriate diet (rats started ~ 100g lighter than they should be at the age reported, and untreated controls gained 3.5-fold less than they should during the study), use of inappropriate and artifact generating fixation methods that likely directly affect the observed degenerative changes, analysis of too few

animals/too small areas for analysis etc., and compromise the reliability of the work as a basis for classification (for further details see document 90019521 and 90019520 respectively). Access to the remaining two reports (Bhide 1991 TOX95-00349 and Bhide 1991 TOX 9651099) was requested by Adama to the Rapporteur Member State, involved member states, the data owner as well as DG Sante but could not be timely obtained for analysis. The original authors of these studies have also been contacted, but (based on the author`s feedback) the authors did not keep the reports or any data of the studies on file. As the studies come from the same laboratory, Adama requests ECHA to make these reports available for expert analysis including Adama as one of the Isoproturon notifiers before the classification of Isoproturon is discussed, and to review the reliability of these studies, particularly in regards to the findings of the studies that could be analysed and the fact that in a reliable study with a 4-fold higher dosing no effects on fertility were seen. These studies were conducted almost in parallel by the same study director in the same laboratory; thus it is likely that the deficiencies found in the one accessible report (Bhide 1990) are also present in the two studies that Adama could not access. Adama thus requests ECHA to carefully analyse these two reports for suitability as a basis for classification.

**In conclusion**, the only reliable study in the database indicates no reproductive effects at dose levels that are not excessively toxic, and all effects seen in this study on reproductive performance are secondary to maternal toxicity. The other contributions which could be obtained and analyzed do not fulfil appropriate quality standards for classification, and these deficiencies likely apply to the two studies that could not be analysed, as they were conducted in parallel at the same laboratory by the same study director.
A classification with Reproductive Toxicity Cat. 2 is therefore not justified. Such classification, based on unreliable data, together with the existing Carcinogenicity Cat. 2 classification would mean that the interim criteria for Endocrine Disrupting properties are met. This would result in a hazard-based removal (cut-off) of an active ingredient with a long history of safe use in absence of endocrine activity.
Adama will, despite the formal end of the public consultation, continue efforts to get hold of and analyse the missing two studies (Bhide 1991). Adama has requested an extension of the public consultation period from the EU Commission and is open to provide further analysis if made possible.