16 June 2020
(Presented at MSC-70)

Concerns:	**Annex XV proposal for identification of resorcinol (EC No. 203-585-2) as a substance of very high concern under Article 57 (f) of the REACH Regulation**
Title:	**Minority position of three MSC members who do not agree to the proposed identification of resorcinol (EC No. 203-585-2) as a substance of very high concern under Article 57 (f) of the REACH Regulation**

The Minority Opinion of MSC members from Finland, Italy and Poland on the Proposal for Identification of Resorcinol, EC number: 203-585-2, CAS number: 108-46-3, as a substance of very high concern on the basis of the criteria set out in REACH article 57 (f)

We maintain the conclusion presented in the substance evaluation and the RMOA prepared by the FI CA on resorcinol. In our opinion, the available scientific evidence does not show that resorcinol is a substance of very high concern because of its thyroid disrupting properties, causing probable serious effects to human health, which would give rise to an equivalent level of concern to those of other substances listed in paragraphs (a) to (e) of Article 57. The data in five peer reviewed publications and other information included in the Support Document to the Proposal which were not available at the time of the Finnish substance evaluation and RMOA do not change this position.

Resorcinol inhibits TPO activity in vitro. However, the available data suggests that the efficient and rapid metabolism by first pass metabolism in the liver, prevents resorcinol from reaching systemic concentrations which are toxic for the thyroid gland. The available data do not show accumulation in any organ or tissue, including the thyroid gland. The qualitative data in humans and vitro data support an efficient first pass metabolization and rapid clearance of resorcinol also in humans.

The major element of the SVHC-identification of resorcinol are the medical case reports from 1950 to 1977. Thyroid effects in these medical cases (10 patients) were observed under exceptional exposure conditions, i.e. after using resorcinol containing ointments as a medicine in large quantities over long periods (months to years) to ulcerated skin. Lack of skin barrier and metabolism and the lipophilic vehicle (ointment) used enabled continuous release of unconjugated resorcinol, the active form of resorcinol, to interstitial fluid or directly to vasculature. The exposure route in these medical cases is comparable to subcutaneous route in experimental animal studies representing a non-physiological/artificial exposure route and the lipophilic vehicle (ointment) used potentially changed toxicokinetic of this hydrophilic substance. Although the word exposure is used, these conditions of exposure relate to hazard, not risk conditions. Non-physiological exposure routes are not generally accepted in hazard identification and in regulatory decisions. One of the patients was reported to have intact skin but had renal failure which may have altered the rapid metabolism and excretion of resorcinol.

Several other factors decrease the adequacy, relevance and reliability of these case reports. These include poor reporting, small sample size, history of the individuals is not known (e.g. underlying thyroid dysfunction and many patients were reported to have other clinical issues (e.g. diabetes, heart failure, renal failure, other medical treatments). There is no data to demonstrate the level of exposure to resorcinol (i.e. blood measures). The information on other ingredients in the ointments is reported only in 3 case reports. It is not known how the formulation of the ointments affects the bioavailability and toxicity of resorcinol.

While severe hypothyroidism was reported in these medical cases, animal experimental studies via physiological routes of exposure (diet, drinking water, dermal, gavage) and epidemiological studies on occupational exposure do not indicate clear effects on thyroid gland. Especially the key animal study, two-generation reproductive study (OECD TG 416) shows no consistent effects on thyroid histopathology or weight, T4 or T3 serum concentrations, prenatal or postnatal development, or reproductive parameters (fertility, gestation, oestrus cycle, sperm parameters). Only slight sporadic effects in circulating T3, T4 and TSH hormone levels and in thyroid follicular colloid content are reported. Most of the effects on hormone levels were seen in male rats only without statistical significance. There was no dose-response relationship in any of the effects reported. Altogether, only two reliable animal studies (Cooksey et al. 1985 and Seffner et al. 1995) report data demonstrating thyroid effects via physiological route of exposure. Other data obtained via physiological routes do not support adversity (e.g. two-generation study), are unreliable (inhalation study, Unpublished study report 1977, Samuel 1955, Berthezene et al. 1979), or are negative.

The MSC opinion states that with the validation of AOP (adverse outcome pathway) describing the relationship between inhibition of TPO, decreased T4 and neurodevelopmental alteration due to maternal low T4 concentration (AOP n°42), further

experimental data investigating (neuro)development are not necessary to confirm the effect on motor activity in the preliminary two-generation study. However, no data on resorcinol demonstrate that the substance fits in the AOP42 scheme from the third KER (hence from decreased T4 plasma levels) to the AO (decreased cognitive function): to the best of our knowledge, no data from experimental animal models show a link between resorcinol exposure and effects on the hippocampus. Hence, no data showing: i) decreased T4 in neuronal tissue connected to altered hippocampal gene expression; ii) altered hippocampal gene expression connected to altered hippocampal anatomy; iii) altered hippocampal anatomy connected to decreased cognitive function. Such effects are considered key events in the AOP42 to connect altered thyroid hormone levels to the indicated AO. Indeed, no studies suggestive of a decreased cognitive function has been reported besides to speculate that resorcinol-induced hypothyroidism will do it.

In conclusion, although the exceptional exposure conditions in medical cases do not explicitly contradict with the wording of WHO definition, these conditions weaken the relevance of this data for hazard identification, ED identification and for ELoC assessment. We also consider the confounding factors recognized in these human cases as a shortcoming that decreases the reliability and relevance of the data. The available experimental animal studies via physiological exposure routes do not provide enough evidence to support the conclusion on the adverse effects on thyroid. Therefore, the animal data do not demonstrate that adverse effects on thyroid in human cases would not be specific to these exceptional conditions of exposure. Moreover, there are no experimental model data to demonstrate that resorcinol fits in the AOP42 scheme missing any direct link between resorcinol exposure, or resorcinol-dependent alteration of T4 plasma levels, to adverse effects on the hippocampus' key events up to the AO, suggesting that the resorcinol-dependent decreased cognitive function is a working hypothesis not supported by the eventual resorcinol-induced hypothyroidism.

Therefore we are of the opinion that the available scientific evidence does not show that resorcinol is a substance of very high concern because of its thyroid disrupting properties, causing probable serious effects to human health, which give rise to an equivalent level of concern to those of other substances listed in paragraphs (a) to (e) of Article 57.