Short report from Danish Working Environment Authority´s (AT) Occupational exposure limit quality committee. Evaluation of the report: Pyridine Scientific basis for setting a health-based occupational exposure limit. Report is from 2023.

Members of the quality committee: Frederikke Juul Tidselholdt (Environmental Protection Agency); Anoop Kumar Sharma (Technical University of Denmark-National Food Institute); Zara Ann Stokholm (Aarhus University - Department of Clinical Medicine); Lisbeth E Knudsen (University of Copenhagen - Department of Public Health).

This report is based on a meeting 27th January 2025 arranged by The Danish Working Environment Authority, where the results from the report were discussed after the authors from the working group at NRCWE (Anne Thoustrup Saber and Ulla Vogel) presented the content of the report. After the presentation, the members of the quality committee asked questions to the authors.

This report reviews data relevant to assessing the hazards of pyridine in humans and in animals. Toxicokinetics is briefly described, and previous risk assessments pyridine are summarized. The scientific basis for setting an occupational exposure limits (OEL) are presented. The current Danish OEL (TWA 8h) for pyridine is 15 mg/m^3. The working group evaluated the relevant literature on pyridine from both epidemiological and animal studies. However, since no suitable human studies were identified, endpoints were based on animal studies. The working group regards pyridine-induced liver cancer and lesions in the nose as critical effects. The evidence for a non-threshold mechanism of action for cancer is weak. However, since a non-threshold mechanism-of-action for pyridine-induced cancer cannot be excluded, the present working group considers pyridine-induced cancer in mice as non-threshold mechanism. The current working group calculated an excess of cancer incidences for 1:1,000 at 57 µg/m^3 and 1:10,000 at 5.7 µg/m^3. The working group considers pyridine-induced nose lesions in rats as a threshold effect. A DNEL was calculated, based on a 4-day inhalation study in rats. This results in a DNEL at 11 µg/m_3 for olfactory mucosal lesions. The working group notes that the study on changes in the nose mucosa is based inhalation exposure, which is the occupationally relevant exposure route while the cancer risk estimates are based on oral exposure of mice. This means that the risk estimates based on the cancer study come with additional uncertainties due to 1) the use of a different exposure route than what is relevant in an occupational setting, and 2) an unclear mechanism-of-action for genotoxic effects. On that background the present working group is of the opinion that both risk estimates should be taken into account.

Editorial and minor comments

In the Introduction: Literature research: will be performed change to was performed.

Chemical and physical properties: Include the acid dissociation constant of pyridine.

Manufacture and use: mention the production volume of pyridine in Denmark. Mention the odour threshold also.

The reference to REACH should be more precise and the reference should be mentioned in the reference list.

Human exposure:
The concentration of pyridine in orange juice by D'Souza et al., 1980; Damani et al., 1982 is different:

i. In a very small oral study with two male volunteers receiving 3.4 mg [14C]-pyridine in orange juice (approximately 0.05 mg/kg), about 65% and 68% was recovered in the urine 24 hours after exposure, mostly in the form of the metabolite pyridine-N-oxide (D'Souza et al., 1980; Damani et al., 1982).

ii. In a very small oral study, two male volunteers received pyridine at a dose of 3.4 mg of [14C]-labelled pyridine (~0.04 mg/kg bw) in orange juice (D'Souza et al., 1980; Damani et al., 1982). Twenty-four hours after exposure, 65% and 68% of the dose was recovered in urine of the two volunteers. Two main metabolites were identified: pyridine N-oxide, which accounted for 32% of the dose, and N-methylpyridinium ion, accounting for 6 and 12% of the dose, respectively, for the two volunteers. Approximately 25% of the dose was not characterized (D'Souza et al., 1980; Damani et al., 1982).

iii. Two volunteers received 3.4 mg [14C]-pyridine in orange juice (approximately 0.05 mg/kg) and after 24 hours N-methylpyridinium ion (approx. 5.5% and 12% of the dose) was identified in urine (D'Souza et al., 1980). Pyridine-N-oxide was also detected, accounting for 32% of the administered dose (Damani et al., 1982)).

The reported concentration of pyridine in orange juice should be the same throughout the report and use the same unit.

Occupational exposure levels: A wide range in change to “A wide range of… “

Cancer studies: “increasing to 2.1 after 15 years”, include the 95% CI for the SMR value of 2.1.

Animal studies: Long-term studies: Change to long-term exposure and this is a header and should be in bold.

Non-neoplastic effects: “An overview of the non-neoplastic lesions are presented in Table x”, write the table number.

Previous evaluations of pyridine: ” Although the authors identified one human long-term exposure study, the data could not be used for hazard assessment because the doses were too high and the

participants were epileptic patients who used pyridine as drug for anticonvulsant treatment" and the reference is missing.

Comments on the OEL

In the executive summary, the quality committee, suggest mentioning that no human studies were identified on reproductive and developmental effects.

At the meeting, it was decided that the quality committee would run QSAR modelling (Danish (Q)SAR Database, https://qsar.food.dtu.dk) to get information of the prediction of genotoxicity data of pyridine, because the experimental evidence of pyridine genotoxicity is extremely weak. The QSAR modelling show that both *in vitro* and *in vivo* genotoxicity endpoint predictions are by far mostly negative. Therefore, the quality committee suggests using the threshold effect for cancer, DNEL value of 40 µg/m^3 together with the DNEL at 11 µg/m^3 for olfactory mucosal lesions as occupational exposure limits.