5. Summary of Data Reported and Evaluation

5.1 Exposure data

N-Nitrosoguvacoline, *N*-nitrosoguvacine and 3-methylnitrosopropionitrile have been found in the saliva of betel-quid chewers. Thus, there is some evidence that chewers are exposed to these compounds.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Following subcutaneous administration of 3-methylnitrosaminopropionaldehyde to rats, the incidence of lung adenoma and adenocarcinoma was significantly increased in both males and females. A variety of other benign and malignant tumours was also observed.

Application of 3-methylnitrosopropionitrile to the oral cavity of male rats produced adenomas and adenocarcinomas in lung and nasal cavity, adenomas and carcinomas in the liver and papillomas in the oesophagus and oral cavity.

Subcutaneous administration of 3-methylnitrosaminopropionitrile to rats induced papillomas and carcinomas of the oesophagus and the tongue and papillomas of the nasal

cavity in males and females in a short-term experiment, and an increased incidence of nasal carcinomas in male and female rats and of liver tumours in male rats in a long-term experiment.

In an initiation–promotion study on mouse skin, initiation with 3-methylnitrosopropionitrile led to the development of skin tumours and lung adenomas.

Addition of *N*-nitrosoguvacoline to the drinking-water of rats induced pancreatic adenomas in males in one study, but no increase in tumours in males or females in another.

5.4 Other relevant data

N-Nitrosoguvacoline and *N*-nitrosoguvacine are metabolized in rats to *N*-nitrosonipecotic acid, which is excreted in the urine. *N*-Nitrosonipecotic acid has been detected in the urine of hamsters treated with areca nut plus nitrite, indicating the endogenous formation of *N*-nitrosoguvacoline and *N*-nitrosoguvacine.

3-Methylnitrosopropionitrile induced liver toxicity in female rats.

N-Nitrosoguvacoline but not *N*-nitrosoguvacine was mutagenic to bacteria. 3-Methylnitrosaminopropionitrile caused single-strand breaks and DNA–protein cross-links in human buccal epithelial cells. DNA methylation and cyanoethylation were observed in rats treated with 3-methylnitrosaminopropionitrile. These studies demonstrate that *N*-nitrosoguvacoline, *N*-nitrosoguvacine and 3-methylnitrosaminopropionitrile are genotoxic.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of *N*-nitrosoguvacoline, *N*-nitrosoguvacine and 3-methylnitrosaminopropionitrile.

There is *sufficient evidence* in experimental animals for the carcinogenicity of 3-methylnitrosaminopropionitrile.

There is *limited evidence* in experimental animals for the carcinogenicity of 3-methylnitrosaminopropionaldehyde.

There is *inadequate evidence* in experimental animals for the carcinogenicity of *N*-nitrosoguvacoline and *N*-nitrosoguvacine.

Overall evaluation

N-Nitrosoguvacoline is *not classifiable as to its carcinogenicity to humans (Group 3)*.

N-Nitrosoguvacine is *not classifiable as to its carcinogenicity to humans (Group 3)*.

3-Methylnitrosaminopropionitrile is *possibly carcinogenic to humans (Group 2B)*.

3-Methylnitrosaminopropionaldehyde is *not classifiable as to its carcinogenicity to humans (Group 3)*.