COMMITTEE PAPER FOR DISCUSSION **ACNFP/113/2**

ADVISORY COMMITTEE ON NOVEL FOODS AND PROCESSES

1-METHYLNICOTINAMIDE CHLORIDE

Issue

The Committee is invited to consider whether the response provided by the applicant addresses the concerns raised at the June meeting, and the views of Members with expertise in toxicology and nutrition in regard to the 28 day feeding study.

Background

1. This application, submitted to the UK on behalf of Pharmena SE of Poland, is for food supplements containing for methylnicotinamide chloride (1-MNA), which is a novel food in the EU.
2. When the Committee considered this application at its meeting in June (paper ACNFP/111/3) Members highlighted the following issues:
    a) The metabolic pathway for 1-MNA is not fully elucidated and the levels proposed were significantly higher than would typically be present in the body. 1-MNA is structurally similar to key cellular components NADP-NAD and Members requested further information regarding potential interference with the metabolism of niacin and related compounds.
    b) The half-life of 1-MNA in rats is in excess of 24 hours and, if it was of a similar duration in humans, this could lead to accumulation.
    c) The implications of the gender differences observed in one of the human studies, whether 1-MNA could interact with pharmaceutical products such as statins and whether it could be safely consumed by individuals who are also consuming high doses of niacin to reduce cholesterol.
3. The Committee also advised that it would require additional time to scrutinise the results of a 28-day rat feeding study with 1-MNA before deciding what conclusions can be drawn from these data, in particular the presence of liver lesions in rats given high doses of 1-MNA.
4. The Secretariat contacted the applicant regarding the concerns listed above (letter attached at **Appendix 1**). The Secretariat has also sought advice from the medicines regulator, MHRA (the Medicines and Healthcare products Regulatory Agency) whether products containing 1-MNA would be classed as medicines in the UK. The MHRA confirmed that that it did not consider 1-MNA to be medicinal and, assessment as a novel food is therefore required before it can be marketed in the EU as a food supplement.

5. The applicant's response is attached at **Appendix 2** and is summarised below.

a) metabolic pathways

6. The applicant has provided additional information in regard to the metabolic pathways for 1-MNA and notes that there are specialised physiological systems which transport charged substances such as 1-MNA in contrast to nicotinamide which enters cells by passive diffusion and/or organic cation transporters.

b) half-life and accumulation

7. The applicant highlights a number of studies that measure endogenous plasma concentrations of 1-MNA in health humans and which show variable levels ranging from 9.7–36.7 ng/ml plasma. The applicant notes that in the 28 day rat study 1-MNA was well tolerated despite exposure being 20x greater than endogenous levels in rats (which equates to 1000x greater in humans. In addition the applicant highlights their two single dose human studies which demonstrate exposure of 1-MNA 10x higher than endogenous levels does not give rise to any adverse effects and, using a simulated plasma profile, postulates that 1-MNA levels will return to baseline following supplementation well before 24h due to the relatively short plasma half-life of 3.4 hours.

8. A 10 week study was commissioned by the applicant to investigate the safety and effect on lipid profile parameters following combined administration of statins and 1-MNA. The findings of this study indicated that 1-MNA and 90mg/day statins was safe and well tolerated. In regard to whether 1-MNA can be safely consumed by people who are consuming niacin to lower blood cholesterol the applicant summarised a number of studies which, in their view, demonstrate that additional exposure from 1-MNA would not be a cause for concern if individuals were also on high dose niacin medication.

c) gender differences

9. In regard to the apparent gender effects the applicant notes that this aspect was considered by the FDA when they considered an application for a nicotinic acid pharmaceutical product. This review noted that the differences appeared to relate to the rate of metabolism but that recovery of niacin and its metabolites in the urine was similar in both males and females. For 1-MNA, the applicant notes that a gender effect was only seen at a higher dose and suggests that while there may be pharmacokinetic differences between sexes these are not sufficient to require a differing dose for men and women.

d) 28-day feeding study

10. At the meeting in June the Committee also noted the presence of liver lesions in rats given high doses of 1-MNA in the 28 day feeding study. The the applicant had sought an independent expert view regarding the significance of these results. The Committee indicated that it needed to review these findings and the

conclusions of the independent expert in more detail and Secretariat has sought the views of a sub-group of ACNFP toxicologists and nutritionists. The sub-group have indicated that they are not minded to accept the conclusions of the independent expert and do not regard the no observed adverse effect level (NOAEL) of 500mg/kg/12h to be correct. The Members advised that the independent expert's rationale for discounting the relevance of the necrotic lesions is unclear and this, coupled with other potentially adverse findings in the original study indicate that a follow up 90 day animal study should carried out to investigate all observed effects in more detail. The sub-group's comments are set out below:

	Observed Effect associated with 1-MNA	**Members' view**
1	An increase in calcium and an increase in leukocytes in the male rat urine. Decrease in urine pH.	Could be an adverse effect.
2	The presence of necrotic foci is an undisputable finding and the report authorise suggest that they could be treatment related as there are no present the control groups. The conclusion in the expert opinion is that the reason for their presence is unknown and it is unlikely that they are related to 1-MNA.	Do not accept the expert view that the necrotic foci can be discounted
3	Higher and more variable levels of aminotransferase (AST) and alanine aminotransferase (ALT). . The conclusion in the expert opinion is that this is seen in all study animals and is due to an underlying problem in the animals.	Possibly, but this view requires additional investigation (as noted by the study authors).
4	Report indicates that rats may not have been able to tolerate 1000mg/kg/day in a single dose but C_{max} values would be different if the daily dose administered to the animals was 2x500mg rather than 1x 1000mg/kg/day and this could impact on the NOAEL.	Requires additional investigation.
5	Statistically significant changes in organ weights (absolute and relative to body weight) were regarded to be accidental as they were not treatment related or confirmed histopathologically.	As anomalies only occurred in treatment groups, and the observed findings should not require confirmation by tissue histology. This could be an adverse effect.
6	Effect of withdrawal from high dose treatment on latency of pain response in male rats different to that observed in female rats.	Could be an adverse effect. Differences cannot be discounted because it didn't occur in main study and hypersensitivity cannot be ruled out.

7	Gender specific effects on haemoglobin and mean Corpuscular Haemoglobin Concentration (MCHC) in treatment groups.	Could be an adverse effect. Validity needs to be assessed, possibly by further investigation.
	General observation: Some study findings were not subjected to an appropriate statistical analysis and, at times, it unclear whether the observed effect is dose related.	-

Committee Action Sought

11. The Committee is asked whether the response from the applicant is sufficient to address its concerns in regard to the issues raised at the June meeting.

12. If not, the Committee is asked to indicate what additional information would be required.

13. The Committee is also asked whether they have any comments on the conclusions of the sub-group in regard to the 28 day feeding study and the view of the independent expert.

Secretariat
November 2013

Appendices attached

Appendix 1 Email to applicant setting out Committee concerns

Appendix 2 Response from applicant