Item 5: Review of risks arising from the infant diet and the development of atopic and autoimmune disease: Systematic review C Part I – the role of hydrolysed cows' milk formula in influencing the development of atopic or autoimmune disease – TOX/2015/24 – RESERVED BUSINESS

20. The Chair declared a non-personal, non-specific interest in this item as he was employed at the same institution as the contractors who had performed the review. This was not considered a conflict and Members were content for him to chair this item.

21. This item was considered as reserved business because the results of systematic review C part I had yet to be accepted for publication in the peer reviewed literature.

22. The FSA had commissioned Imperial Consultants to carry out a systematic review of the literature looking at the role of hydrolysed cows' milk formula in influencing the development of atopic and autoimmune disease. This had been carried out alongside, but separate to, three further reviews looking at the infant diet and the development of atopic and autoimmune disease. These had been commissioned in support of the SACN subgroup on Maternal and Child Nutrition (SMCN) review of UK government recommendations on breastfeeding and the introduction of solid foods in the diet.

23. Professor Ian Kimber and Dr Paul Turner were present to provide the Committee with additional expertise on allergic and atopic disease. The contractor who had prepared the review, Dr Robert Boyle from Imperial College, London, was also present to advise the Committee, along with his colleagues Dr Vanessa Garcia-Larsen and Dr Marialena Trivella.

24. Dr Boyle gave a presentation outlining the methodology used in the systematic review and the findings of the review. Data on autoimmune diseases were available only on Type 1 diabetes mellitus. Dr Boyle highlighted that the vast majority of studies were carried out in high risk populations and not the general population.

25. Dr Boyle also commented that most studies reporting allergic outcomes had a high or unclear risk of bias and conflict of interest. There had also been evidence of publication bias in atopic dermatitis and recurrent wheeze studies.

26. Dr Boyle provided an overview of existing reviews and recommendations in this area and explained why this systematic review may have reached different

conclusions from some other reviews on the role of hydrolysed formula in preventing allergic or autoimmune disease.

27. Members were complimentary of the report. The Committee agreed with the conclusions of the review that there was no evidence to support a link between exposure to extensively or partially hydrolysed cows' milk formula and subsequent development of food allergy or type 1 diabetes mellitus. Dr Boyle highlighted that a lack of studies on endpoints other than allergy and type 1 diabetes mellitus meant that no conclusions could be drawn in these areas. The degree of hydrolysation did not appear to have an impact on the role of hydrolysed formula in influencing allergic or autoimmune disease. The evidence concerning the effect of milk fraction (casein vs whey) on atopic or allergic disease had been limited and made up of small studies, but did not suggest a role of milk fraction on the development of atopic or autoimmune disease. In response to Members' questions on whether the heterogeneity of results could be due to timing of assessment rather than the intervention applied, Dr Boyle considered that there was no definitive evidence either way. Members also asked for clarification on whether changes in populations may affect the results. Dr Boyle stated that each meta-analysis had been ordered by year to allow any trends to be identified more clearly. The designs had changed over time. Earlier smaller studies had tended to report a positive effect for hydrolysed formula on influencing allergic and autoimmune disease. However, later studies were larger and have tended to report that hydrolysed formula did not have any influence.

28. The COT considered that the evidence available did not give sufficient basis for recommending further research in this area.

29. A draft Statement would be prepared for the Committee to consider at its next meeting.

Item 7: Final report of the Lead Ammunition Group – TOX/2015/27 – RESERVED BUSINESS

30. Members were informed that Dr Benford was a member of the EFSA CONTAM panel at the time lead was being discussed and that Professor Boobis was the Chair of the lead sub-group.

31. This item was taken as reserved business as the Lead Ammunition Group (LAG) report has not yet been published.

32. The LAG was an independent body which had been established in 2010 to advise the FSA and Defra on the risks to wildlife and to human health of spent lead ammunition. The final report of the LAG had now been received. The COT were

asked to comment on the human health aspects of the LAG report; the wildlife aspects of the report were separately being peer-reviewed via Defra.

33. Current FSA advice was that regular consumers of game shot with lead should reduce their consumption and that this advice was particularly important for vulnerable groups such as infants and young children, and pregnant women and women trying for a baby, as lead exposure could harm the developing brain and nervous system.

34. As part of the LAG review, two risk assessments had been commissioned covering risks to the health of UK consumers from lead derived from ammunition.

35. The first of the risk assessments had considered the effects on human health from lead exposure via ingestion of game shot with lead ammunition (lead bullets or lead shot) and had drawn on the 2010 opinion of the EFSA CONTAM panel and a 2012 paper by Green and Pain. This had concluded that non-trivial health effects could occur in regular consumers of lead-shot game, particularly of gamebirds. The second risk assessment had considered consumption of products derived from livestock which had fed or foraged in areas of lead gunshot deposition. It had been considered possible that consumer exposure to lead could occur to a limited extent via red meat or milk, but hazardous lead levels in eggs and chicken meat had been documented where chickens had foraged in areas of high lead deposition.

36. The primary route of exposure to lead had been from game shot with lead ammunition, particularly gamebirds or small game killed with lead shot, since this was more likely to break up on impact, resulting in small lead fragments that were not apparent and not removed during food preparation. Exposure from the meat of livestock foraging from areas where lead had been deposited had also been of concern, since uptake by birds and subsequent transfer to eggs had been documented. The Committee considered that high individual intakes could potentially occur from consumption of meat or eggs from occasional heavily contaminated birds, and would be of greater concern in individuals who were regularly consuming produce from the same, contaminated, source. Although there were data on uptake from chickens foraging on shot-over land, Members asked if sheep might also be a source of exposure.

37. Reports of lead poisoning in livestock following ingestion of metallic lead had been documented but other animal data indicated that lead occurred at higher levels in offal rather than muscle tissue. However, it was possible that secondary exposure from lead might be more of a concern than had been reflected in the report.

38. As had been discussed in the LAG report, the population at risk of high lead exposure from consumption of game was a very specific one. The general

population, who only occasionally consume game shot with lead, would be at low risk. The high consumers were recreational shooters and their families and individuals who worked in the shooting industry, some of whom reportedly consumed up to 5 game meat meals a week. The available data had been limited but two independent surveys of consumption in this population had arrived at similar estimates. The size of the population could be in the tens of thousands but the Committee considered that the upper estimate of hundreds of thousands of consumers was much less certain. It was unclear how much of the game consumed would have been shot with lead ammunition, though this uncertainty was more applicable to venison, some of which was farmed.

39. Members agreed that it would have been helpful if there had been a study which linked exposure from lead-shot game to blood lead levels in UK consumers, although data from other countries had been included in the assessment. The LAG report stated that such a study had been proposed by some LAG members, but this had not been taken up by stakeholders given the LAG's "emerging investigations and plans."

40. The LAG report had discussed benchmark dose modelling, which had been carried out by EFSA and by Green and Pain (2012). The benchmark responses (BMRs) which had been identified and used in modelling by EFSA had included reduced intelligence and cognitive function in children, and cardiovascular effects and chronic kidney disease in adults. In addition, the risk assessment by Green and Pain (2012) and also considered by the LAG, had modelled a 1% increase in the risk of spontaneous abortion in pregnant women. It had been unclear how robust this BMR was as the nested case-control study it was based on was small, comparing 35 cases and 60 controls and only a 1% increase in the rate of spontaneous abortion had been modelled, whereas for some of the other endpoints an increase of 10 % in the response had been modelled. It was likely that neurotoxicity, particularly in children, was the most important end point.

41. The Committee was unconvinced by the argument supporting the use of a BMD rather than a BMDL as the uncertainties around the bioavailability of lead could have been accounted for by adjusting the exposure assessment. It was agreed that there was a lack of data on the bioavailability of metallic lead. The LAG reported that the bioavailability of metallic lead might be 40% lower than the value used in the EFSA analysis. However, it was noted that the authors had attempted to address the uncertainties in bioavailability by presenting the quantities of game meat consumption (and thus lead exposure) associated with a particular BMR end point as a range. A sensitivity analysis, examining how much game could be reasonably consumed, had not been conducted.

42. Overall, the committee was in agreement with the conclusions drawn by the LAG but had reservations regarding the quantitative aspects. Since specific quantities of game meat consumption were not recommended in the LAG report, it was agreed that the report did not affect the current FSA advice on the consumption of game shot with lead ammunition.