APPENDIX A: Multi-Active Ingredients Product Analysis

The Agency does not routinely include, in its risk assessments, an evaluation of mixtures of active ingredients, either those mixtures of multiple active ingredients in product formulations or those in the applicator's tank. In the case of the product formulations of active ingredients (that is, a registered product containing more than one active ingredient), each active ingredient is subject to an individual risk assessment for regulatory decision regarding the active ingredient on a particular use site. If effects data are available for a formulated product containing more than one active ingredient, they may be used qualitatively or quantitatively[1] [2].

Acute oral toxicity data (*i.e.*, LD_{50} values) from mammalian studies for formulated products that contain methomyl and one or more additional active ingredients are summarized in the table below.

Currently, the Agency's guidance for assessing the potential risk of chemical mixtures is limited to human health applications (USEPA, 2000). However, the guidance includes principles for evaluating mixtures to assess potential interactive effects that are generally applicable. Consistent with EPA's Overview Document (USEPA, 2004), the Agency's mixture guidance (USEPA, 2000) discusses limitations in quantifying the risk of specified mixture when there is differential degradation, transport and fate of chemical components following environmental release or application. The LD_{50} values are potentially useful only to the extent that a wild mammal would consume plants or animals immediately after these dietary items were directly sprayed by the product. Increasing time post application, the differential rates of degradation, transport, *etc*. for the active ingredients in the formulation only permit a qualitative discussion of potential acute risk (USEPA 2004).

As discussed in USEPA (2000) a quantitative component-based evaluation of mixture toxicity requires data of appropriate quality for each component of a mixture. In this mixture evaluation LD_{50}s, with associated 95% confidence intervals, are needed for the formulated products. The same quality of data is also required for each component of the mixture. Given that many of the formulated products do not have LD_{50} values of the required quality and since LD_{50} values are not available for all the components of these formulations a quantitative analysis of potential interactive effects is not possible.

While a quantitative evaluation of the data is not possible with currently accepted scientific methods, as a screening tool, a qualitative analysis can be used to indicate if formulated products exhibit interactive effects (*e.g.*, synergism or antagonism). In the case of methomyl, of the formulated products, two products (EPA Reg. No. 2724-274 and 53871-3) have an LD_{50} value and associated confidence intervals. When these product LD_{50}s and associated confidence intervals are adjusted for the percent methomyl (1.1 and 1%, respectively) the adjusted LD_{50} value of 34.2 mg a.i./kg-bw (CI range of 27.8 to 42 mg a.i./kg, MRID 41950001 for the Golden

[1] Overview of the Ecological Risk Assessment Process in the Office of Pesticide Programs, Environmental Protection Agency (January 2004) (Overview Document).

[2] Memorandum to Office of Prevention, Pesticides and Toxic Substance, US EPA conveying an evaluation by the U.S. Fish and Wildlife Service and National Marine Fisheries Service of an approach to assessing the ecological risks of pesticide products (January 2004).

Marlin formulation with EPA Reg. No. 2724-274) is not statistically distinct from the female rat 14-day LD_{50} of methomyl (30 mg a.i./kg-bw; CI range of 23 - 40 mg a.i./kg, MRID 42140101); however, the LD_{50} value of 14 mg a.i./kg-bw (CI range of 11.7-16.8 mg a.i./kg, MRID 44933202 for the Stimukil fly bait with EPA Reg. No. 53871-3) suggests that the formulation is more toxic than the active ingredient alone. Thus, it is reasonable to conclude that an assumption of dose-addition would be appropriate.

Methomyl Products with More than One Active Ingredient[3, 4]

PRODUCT/ TRADE NAME	EPA Reg.No.	MRID	% Methomyl	PRODUCT		ADJUSTED FOR ACTIVE INGREDIENT	
				LD_{50} (mg/kg)[1]	CI (mg/kg)	LD_{50} (mg/kg)	CI (mg/kg)
Golden malrin rf-128 fly killer	2724-274	41950001	1.1	3106	2524-3822	34.2	27.8-42.0
Lurectron scatterbait	7319-6	42679901	1	>4000	No Data	40	No Data
Stimukil fly bait	53871-3	44933202	1	1400	1170-1680	14	11.7-16.8

[1] The LD_{50} data is based on a combined male and female value

[3] From registrant submitted data to support registration. Compiled by Office of Pesticide Programs Health Effects Division.

[4] Methomyl: LD50 = 30 mg/kg ; CI= 23-40 mg/kg.