## Appendix A. Multi-Active Ingredient Product Analysis for Metolachlor and S-Metolachlor

### Metolachlor:

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., LD50 values) from mammalian studies for formulated products that contain metolachlor and one or more additional active ingredients are summarized 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 mixtures when there is differential degradation, transport and fate of chemical components following environmental release or application. The LD50 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 LD50s, with associated 95% confidence intervals, are needed for the formulated product. The same quality of data is also required for each component of the mixture. Given that many of the formulated products do not have LD50 values of the required quality and since LD50 values are not available for all the components of these formulations a quantitative analysis of potential interactive effects is not possible.

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[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).

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 metolachlor, a qualitative examination of the trends in LD50 values, with the associated confidence intervals, across the range of percent active ingredient, show no discernable trends in potency that would suggest synergistic (i.e., more than additive) or antagonistic (i.e., less than additive) interactions. In addition, when the product LD50s, and associated confidence intervals, are adjusted for the percent metolachlor (a conservative assumption that attributes all of the observed toxicity of the formulated product to metolachlor) in 4 out of the 9 cases these adjusted 95% confidence intervals overlap with the confidence values of the LD50 value of metolachlor. In the other instances the adjusted LD50s and/or the confidence intervals are within a factor of 2; given the overall variability of the available acute toxicity data these differences are not considered biologically significant. Based on this qualitative evaluation of the best available data and the Agency's existing guidance it is reasonable to conclude that these formulations are reflecting an independent additive toxicity response and not an interactive effect. Given that the active and inert ingredients would not be expected to have similar mechanisms of action, metabolites or toxicokinetic behavior it is also reasonable to conclude that an assumption of dose-addition would be inappropriate. Consequently, an assessment of metolachor's potential effect when it is co-formulated with other active ingredients can be based on the toxicity of metolachlor.

## Pesticide Products Formulated with Metolachlor and Other Pesticide Active Ingredients[i] [ii]

| | | | PRODUCT | | ADJUSTED FOR ACTIVE INGREDIENT | |
|---|---|---|---|---|---|---|
| **PRODUCT/TRADE NAME** | **EPA Reg.No.** | **% Metalchlor** | **LD50 (mg/kg)** | **CI (mg/kg** | **LD50 (mg/kg)** | **CI (mg/kg)** |
| Drexel trizmet ii | 19713-547 | 26.1 | >=2000 | NA Limit Dose | NA | NA |
| Metolachlor at | 19713-593 | 34.8 | 2000 | NA Limit Dose | NA | NA |
| Triangle Herbicide | 66222-131 | 34.5 | >=2000 | NA Limit Dose | NA | NA |
| Parallel Plus | 66222-132 | 28.9 | >=2000 | NA Limit Dose | NA | NA |
| Bicep II Magnum | 100-817 | 26.1 | 3271 | 2755-3882 | 854 | 719-1013 |
| Bicep Lite II Magnum | 100-827 | 35.8 | 4824 | 3660-6358 | 1727 | 1310 -2276 |
| Bicep Magnum | 100-886 | 26.1 | 4294 | 3284-5615 | 1121 | 857-1466 |
| Boundary Herbicide | 100-958 | 68.1 | 2586 | 2305-2900 | 1761 | 1570-1975 |
| Camix Selective | 100-1148 | 36.8 | >5000 | NA Limit Dose | NA | NA |
| Lumax Selective | 100-1152 | 29.4 | 2865 | No Data (ND) | ND | ND |
| Expert Herbicide | 100-1161 | 18.6 | >=2000 | NA Limit Dose | NA | NA |
| Boundary 6.5EC | 100-1162 | 58.2 | 1805 | 1444-2339 | 1051 | 840-1361 |
| Brawn herbicide | 100-1165 | 26.1 | ND | ND | ND | ND |
| Sequence Herbicide | 100-1185 | 29 | >5000 | NA Limit Dose | NA | NA |
| Newconcept Herbicide | 100-1201 | 19 | 4144 | 1485-20,000 | 787 | 282-3800 |
| Bicep Lite II Magnum | 100-1213 | 35.8 | 4824 | 3660-6358 | 1727 | 1310-2276 |
| Bicep II Magnum | 100-1214 | 26.1 | 3271 | 2755-3882 | 854 | 719-1013 |
| Prefix herbicide | 100-1268 | 46.4 | 5000 | 2865-8390 | 2320 | 1329-3893 |
| Dupont Cinch ATZ Lite | 352-623 | 35.8 | ND | ND | ND | ND |
| Dupont Cinch ATZ | 352-624 | 26.1 | ND | ND | ND | ND |
| Charger Max ATZ | 1381-199 | 0.7 | ND | ND | ND | ND |
| Charger Max ATZ Lite | 1381-208 | 35.8 | ND | ND | ND | ND |
| Stalwart extra | 60063-23 | 26.1 | >=2000 | NA Limit Dose | NA | NA |

**S-Metolachlor:**

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.[3] [4]

Acute oral toxicity data (i.e., LD50 values) from mammalian studies for formulated products that contain S-metolachlor and one or more additional active ingredients are summarized 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 mixtures when there is differential degradation, transport and fate of chemical components following environmental release or application. The LD50 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 LD50s, with associated 95% confidence intervals, are needed for the formulated product. The same quality of data is also required for each component of the mixture. Given that many of the formulated products do not have LD50 values of the required quality and since LD50 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 S-metolachlor, a qualitative examination of the trends in LD50 values, with the associated confidence intervals, across the range of percent active ingredient, show no

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

[4] 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).

discernable trends in potency that would suggest synergistic (i.e., more than additive) or antagonistic (i.e., less than additive) interactions.

In addition, when the product LD50s, and associated confidence intervals, are adjusted for the percent S-metolachlor (a conservative assumption that attributes all of the observed toxicity of the formulated product to S-metolachlor) the adjusted 95% confidence intervals overlap with the confidence values of the LD50 value of metolachlor for two (000100-01201 and 000100-01268) of the eight products that have LD50 values with associated confidence intervals.

To confirm a lack of interactive effects, an alternative approach was used. The LD50s for the formulated products were estimated by considering the proportion and potency of each active ingredient in the mixture using the formula presented below [5], where *r* equals the relative proportion of each active ingredient (ai) in the formulated product (f)

$$\text{Estimated } LD50_{(f)} = [r_{ai1}/LD50_{(ai1)} + r_{ai2}/LD50_{(ai2)}]^{-1}$$

The estimated LD50 formula assumes no synergistic or antagonistic interactions. Estimated LD50 values above or below the LD50 confidence intervals for the formulated product could suggest an interactive effect. In all eight cases, the estimated LD50s fell within the confidence intervals for the formulated products. These results provide additional confidence that synergistic interactions are unlikely for the formulated products examined.

Based on these evaluations of the best available data and the Agency's existing guidance it is reasonable to conclude that these formulations are reflecting an independent additive toxicity response and not an interactive effect. Given that the active and inert ingredients would not be expected to have similar mechanisms of action, metabolites or toxicokinetic behavior it is also reasonable to conclude that an assumption of dose-addition would be inappropriate. Consequently, an assessment of S-metolachlor's potential effect when it is co-formulated with other active ingredients can be based on the toxicity of S-metolachlor.

[5] Methods described in Tabashnik, BE, Evaluation of Synergism among *Bacillus thuringiensis* Toxins, Appl Environ Microbiol. 1992 Oct;58(10):3343-6.

## Pesticide Products Formulated with S-Metolachlor and Other Active Ingredients [iii] [iv]

| | | | PRODUCT | | ADJUSTED FOR ACTIVE INGREDIENT | |
|---|---|---|---|---|---|---|
| **PRODUCT/TRADE NAME** | **EPA Reg.No.** | **% S-Metolachlor** | **LD 50 (mg/kg)** | **CI (mg/kg)** | **A.I Adjusted CI (mg/kg)** | **A.I Adjusted LD50 (mg/kg)** |
| Bicep II Magnum herbicide | 000100-00817 | 26.1 | 3271 | 2755-3882 | 854 | 719-1013 |
| Bicep Lite II Magnum | 000100-00827 | 35.8 | 4824 | ND | 1727 | NA |
| Bicep Magnum | 000100-00886 | 26.1 | 6044 | 4880-7487 | 1577 | 1274-1954 |
| Boundary | 000100-00958 | 68.1 | 2586 | 2305-2900 | 1761 | 1570-1975 |
| Camix | 000100-01148 | 36.8 | >5000 | NA | NA | NA |
| Lumax | 000100-01152 | 29.4 | 2865 | ND | 842 | NA |
| Expert | 000100-01161 | 18.6 | >2000 | NA | NA | NA |
| Boundary(r) 6.5ec | 000100-01162 | 58.2 | 1805 | 1444-2339 | 1051 | 840-1361 |
| Brawn | 000100-01165 | 26.1 | 3271 | 2755-3882 | 854 | 719-1013 |
| Sequence | 000100-01185 | 29 | >5000 | NA | NA | NA |
| Lexar | 000100-01201 | 19 | 4144 | 1485-20000 | 787 | 282-3800 |
| Bicep Lite II Magnum manufacturing use product | 000100-01213 | 35.8 | ND[3] | NA | NA | NA |
| Bicep Lite II Magnum manufacturing use product | 000100-01214 | 26.1 | 3271 | 2755-3882 | 854 | 719-1013 |
| Prefix | 000100-01268 | 46.4 | 5000 | 2865-8390 | 2320 | 1329-3893 |
| Halex gt | 000100-01282 | 20.5 | >5000 | NA | NA | NA |
| Dupont Cinch Atz Lite | 000352-00623 | 35.8 | 3621 | ND | 1296 | NA |
| Dupont Cinch Atz | 000352-00624 | 26.1 | 4824 | ND | 1259 | NA |
| Charger Max Atz | 001381-00199 | 26.1 | ND[4] | NA | NA | NA |
| Charger Max Atz Lite | 001381-00208 | 35.8 | ND[3] | NA | NA | NA |

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

[ii] Metolachlor: LD50= 2514 mg/kg; CI= 2084 to 3126 mg/kg

NA= Not applicable; ND= No data

[iii] From registrant submitted data to support registration. Compiled by the Office of Pesticide Programs Registration Division and Health Effects Division.

[iv] S-metolachlor LD50=2672 mg/kg; CI= 2149-3322 mg/kg

[3]Product similar to 000100-00827

[4]Product similar to 000100-00817

NA= Not applicable; ND= No data