

EXHIBIT 89

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Clustering glyphosate formulations with regard to the testing for dermal uptake

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1. Scope

Operator exposure assessments are part of an ANNEX III dossier, supporting the registration of a pesticide formulation in member states of the European Union. In this assessment default model settings, data assumptions and scenarios can be used (Tier I assessment) or more scenario specific and product/formulation-related data can be selected in order to refine the assessments and ~~turn~~ make the risk evaluation more realistic.

One of the product specific parameters that can make a big difference in the exposure assessment is the dermal uptake factor, ~~this~~ which is the fraction of the amount of active ingredient on the skin surface that is absorbed by the skin tissue. The current European default value for dermal uptake (~~this is when~~ product specific data is missing) is 10% of the actual exposure (~~the exposure that reached the~~ to uncovered skin) but future predictive models (EUROPOEM) could have a more conservative approach (100% of the actual exposure). When ~~this~~ new predictive models will be ~~also~~ implemented (2002), formulation specific dermal data will be key for a successful risk evaluation.

Glyphosate has a whole series of different formulations. The differences between those formulations are ~~for instance~~ based on:

- * ~~the~~ the different salt types used to formulate the active ingredient, based on
- * ~~the~~ the use of different surfactants and
- * ~~the~~ the quantitative active ingredient/surfactant ratio
- * ~~the~~ the concentrations of active ingredient and surfactants
- or could be based on the presence or absence of other inert ingredients such as anti-foam agents.
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Until today Monsanto has conducted ~~only~~ formulation specific dermal uptake research ~~only~~ on the formulation Roundup (MON 2139). It is clear that because the compositional differences the dermal uptake data for Roundup can't be extrapolated as such towards the wide range of formulations ~~because~~ ~~_____??~~. Every ingredient in a formulation can have a specific influence of dermal uptake. Scientific experimental evidence is necessary.

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Ideally all of the different glyphosate formulations would have to be tested for dermal uptake. It is possible though, by focusing on the key parameters affecting dermal uptake, to compare and group (cluster) the formulations according to their expected behavior on the skin. For each formulation-cluster it will be possible to identify a representative formulation. This formulation could be tested for dermal uptake and the results could then be extrapolated to the other formulations in the same cluster.

Key to this approach is a correct identification of the formulation parameters that will impact the dermal uptake. For the purpose of this exercise we will have to focus on the data that's available in the supporting formulation specific data packages.

Which formulations are to be considered?

The formulations to be clustered are the formulations that will be subject to the European re-registration procedure in 2003 and by consequence have to be supported by an ANNEX III dossier. Existing formulations that will not be supported anymore or that will be supported by a third party are not considered.

Key parameters to be considered when grouping formulations ?

Please note that the description of the key parameters is based on the data that's available from the dossiers. This available data will be the basis for the clustering exercise.

Salt type, Dissociation constant (pKa),

Glyphosate acid exists as a zwitterionic species in a solid state (state 1a) is an acid with and has a relative low a-water solubility in water (Sw) around (1.2 at 25 C)d 12 g/liter. This solubility is too lowhigh- for formulating the active ingredient into a n-emulsifiable concentrate (EC)suspendableoluble liquid (SL) but too highlow for a suspension concentrate (SC). For this reason glyphosate is (in most casesformulations), formulated as a salt. The formulations of interest in this exercise allow to distinguish four three salt types: an isopropylamine salt (IPA), a sodium salt, and an ammonium salt and a potassium salt of glyphosate. The majority of these formulations are is formulated as an IPA salt.

Once the formulation is diluted in water, the salt will dissociate immediately into the free acid (free acid state). As glyphosate consists of an amino group a carboxylic acid group and a phosphonic acid group, the dissociation of the free acid state of glyphosate happens in 3 sequential phases each characterized by a pKa value. In a first phase the carboxylic acid group will dissociate into a mono-anion (pK1 = 2.27). In a next step the mono-anion form shifts into the dianion form by dissociation of the phosphonic acid group (PK2 = 5.57). When the amino-group of the dianion form dissociates (pK3 = 10.25) the trianion

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~~form is established. Each dissociation step is characterized by an equilibrium between the two forms and this equilibrium is pH driven. At physiological pH-values the dianion form (dissociated carboxylic and phosphonic acid group) is prevalent. An equilibrium will be established between the dissociated and the non-dissociated form, with a clear shift to the dissociated form.~~

~~Also in the formulation an equilibrium exists between the dissociated and the non-dissociated form with here a clear shift to the non-dissociated form. Common amine surfactants (see further) will further neutralize the glyphosate acid.~~

~~The dissociation state of glyphosate influences its behavior on the skin. For instance zwitterions penetrate the skin more readily than any other form of glyphosate.~~

Using a simplistic approach, the degree of dissociation is driven by the concentration, the pH in the and the dissociation constant (pKa).

Therefore a first basis to group the glyphosate formulations could be the salt type and pH. The same salt type of glyphosate in any formulation will have lead to the same dissociation behavior if the same ?? surfactants are used (see further) and under comparable pH conditions.

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Surfactants

The upper barrier of the skin (epidermis) is very lipophilic. This natural barrier prevents dehydration of the skin and prevents for instance bacteria and other outer micro-elements from entering the body through the skin. Glyphosate on the other hand is very hydrophilic so initially a low interaction between glyphosate and human skin is to be expected. Surfactants are able to increase glyphosate absorption through the skin by (1) removal of lipids (sebum) from the epidermal surface due to surfactant action, (2) increase of the hydration state of the skin (under closed exposure conditions), (3) increase of skin contact (spreading of water droplets by surfactant action), (4) increase of contact time with the skin due to decrease of evaporation of water from the droplets containing surfactant (surfactant monolayer at surface of droplets slows down passage to vapour phase), (5) increase of sub epidermal blood flow due to irritant action of surfactant, (6) intra-epidermal and sub epidermal intercellular water accumulation due to the irritant action of the surfactant. In order to have an interaction between the skin and glyphosate (1) the surface properties of the skin have to be modified (2) a contact area between glyphosate and the skin has to be established, the larger this contact area the more intense the contact and the higher the potential influx of glyphosate (3) the transfer of glyphosate in the skin will be facilitated if glyphosate is in a solubilized stage (advective transport). The longer glyphosate stays solubilized the more intense the contact with the skin. All this elements can be influenced by surfactants. Surfactants will interact with the lipophilic skin surface and will thus alter the properties of the epidermis. This interaction

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~~can consist in delipidization of the epidermis, the surfactant solvent may be absorbed by the skin, altering it's properties or the surfactant could just irritate the skin. The surface tension of droplets enriched with surfactants will be altered in a way that the contact angle between the droplet and the skin will decrease (wetting surface will increase compared to a normal water droplet). The increased contact area creates more potential for interaction between glyphosate and the skin (higher potential influx). Surfactants will change the vapor pressure of mixtures in a way that evaporation of the droplet can be slowed down. As a result a longer interaction between the droplet and the skin is established with a higher/longer potential for glyphosate to interact with the skin.~~

~~All these properties of surfactants lead to a second basis for clustering: the surfactant type. Formulations based on a same surfactant type (and certainly when the surfactant/glyphosate ratio in the formulation is in the same range) will have a comparable interaction and contact with the skin. The second bases for clustering becomes a combination of the surfactant type, the surfactant load, the surfactant/glyphosate ratio and the glyphosate load in the formulation.~~

Anti-foams

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~~(Effect of anti-foam??) Sometimes an anti-foam agent is added to the formulation. Some anti-foams are in general are tensio active agents others are not (e.g. polysiloxanes) so they have also an but in general adding an anti-foam should not have an influence on the over all surface tension of the formulation and the spray liquid. Their concentration is in general much lower than the concentration of the surfactants. Therefore when an anti-foam is added the formulation should be treated in a separate cluster.~~

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Pelargonic acid

Sometimes pelargonic acid is added as a symptomology enhancer.

The addition of pelargonic acid in concentrations greater than that of the surfactant may play a role in glyphosate skin penetration. Since the formulations have been neutralised the pelargonic acid is likely to be present (otherwise not soluble) as the IPA salt which in fact is a soap.

Formulations containing pelargonic acid are clustered separately. When grouping the formulations on this basis and adding the previous clustering criteria (salt type, pKa) formulation groups with an identical pH range (as far as data is available) are obtained as well.

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The results based on these limited criteria are shown in table 1.

Table 1: Glyphosate formulation clusters based on salt type, pKa, surfactant type and pH
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