

Toxicity of agrochemical formulations

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Most agrochemicals have physicochemical properties that make it impractical to apply them directly to crops and other targets. It is necessary to provide a concentrate of the active ingredient, to which formulation agents have been added to allow dilution with water for spraying. These ingredients perform several functions, including emulsifying, solubilizing, antifoaming, and the like. The properties of these materials are not intended to include pesticidal activity. However, some of these materials may have intrinsic toxicologic properties that should be taken into account in an overall evaluation of the safety of the product. In agriculture, exposure to these materials is sporadic and seasonal. The testing of the complete formulation is based on the evaluation of this risk, and it is concentrated on the evaluation of the short-term exposure to the concentrated product. Many of these substances are rather banal and are generally regarded as safe. Exceptions to this rule do exist, particularly concerning solvents; in such cases a fuller data package is necessary to perform risk assessment.

Key terms inert; risk assessment; review; solvent.

Agrochemical products, as sold to the farmer, are formulations of an active ingredient, or several active ingredients, with other materials that enhance the usefulness of the active ingredient. The main function of these formulation ingredients is analogous to excipients in pharmaceutical products (ie, they are not intended to interact with the active ingredient, but only to allow the intrinsic properties to be expressed).

In general, pesticide-active ingredients tend to be solids of low water solubility that are effective from a few grams to a few kilograms per hectare. As a result, it is necessary to disperse the active ingredient in water to allow easy application by spraying equipment in the field. These formulation ingredients allow the active ingredient to be mixed with water as a suspension or emulsion, so that a more dilute product can be effectively applied to the crop. These materials are used for their physicochemical, rather than any biological, properties. For this reason, these substances have been conventionally referred to as “inerts”, to distinguish them from several active ingredients. This convention was never intended to imply that these formulation ingredients were toxicologically inert, only that they were not pesticidally active. Exceptions are synergists and safeners, which are not the subject of this article.

Very few of these materials are manufactured exclusively for agrochemical formulations, and they may

find employment in a wide variety of industrial and domestic settings. As such, data packages have usually been generated on these materials to satisfy a range of legislative requirements under transport and labeling laws, high production volume (HPV) programs, premarketing notifications, and the like. They are not required to be registered in their own right under agrochemical legislation as they are not pesticidally active.

This situation should not be taken to imply that they have been ignored in the regulation of agrochemical products. The history of regulating such materials goes back more than 40 years. The United States Food and Drug Administration compiled a list of inerts currently in use in 1962. This list was subsequently to become known as the “positive list”. In 1969 a process was put in place whereby it became necessary to petition for the inclusion of new compounds. In 1987 the Office of Pesticide Programs established the following four toxicologic levels: (i) inerts of toxicologic concern, (ii) potentially toxic inerts (high priority for testing), (iii) inerts with unknown toxicity, and (iv) inerts of minimal concern.

More recently the United States Environmental Protection Agency (EPA) produced a draft guidance document (1) on the methodology and data needed for safety assessment that envisages the following categories: “a long history of safe usage” (category 1a), “some data needed for . . . confirmation of low or low/moderate

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toxicity" (category 1b), "could not locate sufficient data ... to assess a chemical substance's toxicity" (category 2), and compounds EPA suspects may involve significant toxicity or exposure concerns (category 3). Whereas many inerts are expected to fall into categories 1a & 1b, some will undoubtedly fall in the other two. However, the notion that nothing is known about the major formulation ingredients is manifestly not true, nor is the assertion that they are often more toxic than the active ingredient. The latter claim may, of course, be justified if the active ingredient has negligible toxicity, but it is misleading in its implications.

Types of formulations and their compositions

Formulations can be simple to highly sophisticated. The simpler formulations are typically the emulsifiable concentrates based on an organic solvent, through to sophisticated water dispersible granules and other specialized formulations such as "jumbo granules", microcapsules, and the like. Table 1 shows some of the types of ingredients used, and tables 2, 3, and 4 illustrate the different compositions of some common classes of formulation.

Risk assessment of formulations

The first scenario envisaged in the risk assessment of complete formulations is the accidental and deliberate poisoning of humans or animals. For this reason formulations are tested for acute oral toxicity or, if appropriate, inhalation toxicity. In some cases the solvents can be a significant contributor to the hazard of the product. Hydrocarbon solvents can be very irritant to gastric mucosa and can be very dangerous if aspirated (2).

The second scenario for evaluation is that of agricultural workers (mixers, loaders, and sprayers). As accidental exposure is usually external, the appropriate tests are for dermal toxicity, skin and eye irritation, and sensitization. If appropriate, 28- or (exceptionally) 90-day dermal studies can be performed. It should be noted that most agricultural uses are seasonal and short term. It is exceptional for anyone to be in contact with the same formulation more than a few days a year, or a few weeks in the case of professional applicators (Unpublished report: European Crop Protection Association. Market research of professional field contractors in support of AOEL establishment; 1996).

Dietary exposure from agricultural commodities is not normally evaluated for formulation "inerts", as most of these materials are of very low toxicity when compared

with any likely exposure. Some are also volatile or expected to be degraded in the field.

Specific cases of formulation ingredients

While the foregoing summarizes the general situation, there are some compounds used as formulation ingredi-

Table 1. Examples of "inerts".

Function	Example
Antifoam	Silicone emulsion, nonanol
Antifreeze	Glycols
Binder	Lignosulfonates
Filler	Magnesium aluminum silicates
Dispersing agent	Nonionic or anionics
Dye	Cosmetic or foodstuff list
Emulsifier	Nonionic or anionics
Preservative	BIT, dichlorophen
Solvent	Ketones, aromatics, amides
Thickener	Polysaccharide, cellulose
Wetting agent	Nonionic or anionics

Table 2. Composition of a typical emulsifiable concentrate.

Formulation	Percentage (%)	Function
Active ingredient	20–60	Provide biological activity
Solvent	25–75	Dissolve active ingredient
Emulsifier	3–10	Incorporate into water
Antifoam	0.1–1	Reduce foam

Table 3. Composition of a typical suspension concentrate.

Formulation	Percentage (%)	Function
Active ingredient	40–65	Provide biological activity
Wetting agent	1–3	Ensure hydrophilicity of active ingredient
Dispersing agent	3–7	Prevent flocculation
Suspension agent	2–5	Prevent sedimentation
Antifreeze	5–10	Add cold stability
Antifoam	0.1–1	Reduce foam
Other additives	0.1–5	Add colorings or adhesive quality
Water	35–55	Provide continuous phase

Table 4. Composition of a typical water-dispersible granule.

Formulation	Percentage (%)	Function
Active ingredient(s)	50–90	Provide biological activity
Wetting agent	1–5	Ensure hydrophilicity
Dispersant	3–7	Ensure suspension stability
Binding agent	2–5	Ensure cohesion of granules during transport and storage
Inorganic filler	0–40	Dilute
Other additives	0.1–3	Add coloring or adhesive quality; act as chemical stabilizer

ents that have received an in-depth evaluation of their toxicologic properties and potential risk. It is worth repeating that many of these compounds have multiple applications and that risk assessments for agricultural products do not imply that this is their main use.

Nonyl phenol (ethoxylate)

Nonyl phenol is a nonionic surfactant, widely used in a variety of surfactant, detergent, and cleaning applications. It has been extensively reviewed in the European Union (3) and the United States. In Europe it is classified as "harmful if swallowed" (R22) and "corrosive" (R34). A classification is under discussion for reproductive impairment, as it has been shown to have estrogenic activity in *in vitro* and *in vivo* test systems, although at a level of potency many orders lower than standard estrogens (4).

Uterotrophic assays and reproductive toxicity studies using modern protocols have been performed showing effects consistent with estrogenic activity. No observable adverse effect levels (NOAEL) have been established for all end points that are sufficient to perform risk assessments as necessary. However, the tendency is to move away from these compounds towards other wetting agents where possible, due to their environmental persistence.

N-methyl pyrrolidone

N-methyl pyrrolidone (NMP) is a solvent used in many different industrial applications due to its capacity to dissolve many very hydrophobic substances. As some active ingredients of agrochemicals are practically insoluble in water, it has been extremely useful as a solubilizing agent for formulations.

It has been reviewed by United States, European, and international authorities in recent years (5). It is

Table 5. Margin of safety resulting from the use of an N-methyl pyrrolidone (NMP) containing formulation in seed treatment plants. (NOAEL = no observable adverse effect level)

	Actual exposure	NOEL	Margin of safety
Dermal exposure in mixing, loading and cleaning	0.501 mg/kg a day	237 mg/kg a day; dermal teratology in rats ^a	473 g/kg a day
Inhalation exposure in mixing, loading and cleaning	0.042 mg/kg a day	97.2 mg/kg a day; inhalation teratology in rats ^b	2314 g/kg a day

^a According to Becci et al (6).

^b According to Lee et al (7).

nongenotoxic and also noncarcinogenic in rats, and it produces hepatocellular tumors in mice only, at extremely high doses, which are equivalent to about 1000 mg/kg a day.

As the compound has been shown to have developmental toxicity, a range of different developmental toxicity studies have been performed. Oral developmental studies have been carried out with three species, and studies by inhalation and dermal routes are also available. Likewise multigeneration reproduction studies by oral and inhalation routes have been conducted, so that risk assessments for all relevant scenarios can be performed.

Table 5 shows the result of a risk assessment for a seed treatment formulation containing NMP. It demonstrates adequate margins for the end points of concern. This risk assessment is based on studies of exposure to agrochemicals during the treatment of seeds in the normal commercial manner (8). Nevertheless, despite the favorable outcome of the risk assessment, there is a tendency in the industry to move away from this material when an adequate replacement can be found.

Aromatic hydrocarbon solvents

The main solvents used in formulations are called heavy aromatic solvents and have largely replaced such materials as xylene, toluene, and the like, which are considered to represent an unacceptable risk due to flammability. These more modern products have a significantly higher flashpoint and lower volatility, making the storage of large quantities of formulated product considerably less dangerous. The specification calls for a benzene content of less than 0.1% and an aromatic content of greater than 98%.

These are in fact a family of complex mixtures obtained from different cuts of petroleum distillates. An extensive data package exists on the group of products to support their safe use. They are of low hazard with respect to acute exposure as they are of low oral and dermal toxicity and not genotoxic (9).

These heavy aromatic solvents can contain up to 10% naphthalene, which is a ubiquitous industrial product (the active material of mothballs). Nevertheless, naphthalene was recently tested by the national toxicology program (NTP) in lifetime inhalation studies and was shown to cause tumors in rodents. In mice, tumors were observed in the lungs of females. For rats, there was a positive trend towards tumors in the olfactory epithelium (table 6) (10). In 2002 the International Agency for Research on Cancer (IARC) reviewed the data on naphthalene (11) and concluded that the proposed mechanism of action of naphthalene is that the higher

Table 6. Naphthalene carcinogenicity in F344 rats: neoplastic lesions of the nose following inhalation exposure to naphthalene for 2 years.

	Males								Females							
	0 ppm (N=49)		10 ppm (N=49)		30 ppm (N=48)		60 ppm (N=48)		0 ppm (N=49)		10 ppm (N=49)		30 ppm (N=49)		60 ppm (N=49)	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Respiratory epi- thelium adenoma																
Overall rate	–	.	6	12	8	17	15	31	–	.	–	.	4	8	2	4
Adjusted rate ^a	–	.	–	15.3	–	20.6	–	38.1	–	.	–	.	–	9.8	–	5.2
Olfactory epi- thelium neuro- blastoma																
Overall rate	–	.	–	.	4	8	3	6	–	.	2	4	3	6	12	24
Adjusted rate ^a	–	.	–	.	–	10.1	–	7.7	–	.	–	5.1	–	7.2	–	28.2

^a After adjustment for mortality.

rates of metabolism lead to cytotoxic metabolites in mouse lung, causing increased cell turnover and tumors. The high rates of metabolism in rat nasal epithelium similarly leads to tissue damage and nasal tumors; however, the etiology of the nasal tumors is not yet fully understood. IARC has classified naphthalene as a 2B carcinogen. In addition, it has been recently classified as R40 in Europe (Unpublished report: European Commission, European Chemicals Bureau. Meeting of the Commission Working Group on the Classification and Labelling of Dangerous Substances. European Commission, European Chemicals Bureau; 2001.)

The recent review by the European Commission Committee for Toxicity, Ecotoxicity and the Environment concluded that the mechanism of tumor formation was closely linked to chronic inflammation, although they noted that epoxide formation (demonstrated in vitro) may also be involved (12). The intermittent nature of exposure to naphthalene through the use of agricultural formulations makes these findings of doubtful relevance for applicator risk; nevertheless, the feasibility of replacement with naphthalene-depleted aromatic solvents is being studied.

Research on naphthalene has indicated that there are species differences in metabolism and toxicity (13). In comparing the metabolism of naphthalene among species, the maximal rates of metabolism measured in human lung microsomes are about 10–100 times lower than those in mice. In addition, a recent review on the genotoxicity of naphthalene showed no evidence of naphthalene-induced gene mutations, and, when considered with the cytotoxic events, the mechanism of tumor induction in rodents appears to be driven by cytotoxicity and cell regeneration (9). Given the species differences in metabolism and toxicity and the lack of genotoxicity of naphthalene, it is unlikely that the experimental findings in rats exposed to naphthalene indicate a risk for users of these formulations.

Ethylene and propylene glycols

Another component of agrochemical formulations containing water is an antifreeze ingredient. In the past, the most commonly used was ethylene glycol, the same as used in automobile cooling systems. However, the tendency now is to develop formulations using propylene glycol in its place. Table 7 indicates the hazard reductions expected from this voluntary change.

Discussion

Unlike active ingredients of agrochemicals, formulants are not subject to registration under agrochemical legislation. This situation does not mean they are unregulated or that nothing is known about their toxicology. In general, they are regulated under various applicable laws concerning chemicals, and it is rare that these substances have agrochemical formulations as their main

Table 7. Comparison of the hazard of propylene and ethylene glycols. (NOAEL = no observed adverse effect level)

Hazard	Acute poisoning in humans	Animal developmental effects
Ethylene glycol	Human case studies have reported deaths caused by ethylene glycol; well-defined clinical stages: stage I (central nervous toxicity), stage II (cardiopulmonary toxicity), stage III (renal toxicity stage by accumulation of glycolic metabolized to oxalic acid, which forms oxalate crystals)	Ethylene glycol administered by the oral route showed malformations, skeletal abnormalities in the skull, sternebrae and ribs; by inhalation exposure developmental toxicity included exencephaly, low set ears, cleft palate and ventricular defects
Propylene glycol	No reports of lethality; no clearly defined clinical toxicity syndrome	The NOAEL corresponded to the highest tested dose; no differences in numbers of fetal abnormalities (soft tissue or skeletal) were noted

use. In most cases, they are widely used industrial chemicals. Guidance is, nevertheless, being developed in the United States and Europe to specify certain data requirements for the use of these compounds in agrochemical formulations, as it is for pharmaceutical excipients (14).

As a general rule, the testing of complete formulations is concentrated on the acute hazard to users resulting from accidental exposure during handling. This information is required for classification and labeling, which is hazard-based rather than risk-based. Such information is used to recommend protective clothing that will have an impact on the likelihood and extent of exposure.

Additional evaluation of individual formulation ingredients follows the principles of risk assessment and must take into account the frequency and extent of expected exposure. In many cases, generic models of typical agricultural uses are available to help with this assessment [15, 16, unpublished report: Predictive Operator Exposure Model (POEM). Salahud din PSD; 1993].

When hazardous compounds are present in formulations, they are being voluntarily substituted by less hazardous materials when suitable technically and economically viable alternatives exist. Where suitable alternatives do not exist, a risk assessment using realistic exposure estimates or measurements is appropriate for evaluating the acceptability of use.

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