Product Chemistry Tips for Conventional Chemicals

General:

- When in doubt, consult with the team leader in product chemistry.
- Follow the table of data requirements, page 16 in the guidelines and chapter IV in the SOP (Reference #11). http://www.epa.gov/oppfead1/guidance/product-sop.htm#_1_4
- Cover letter should explain briefly what is needed. [Do not provide superfluous information that can be obtained from the data or label and CSF, e.g. product safety, efficacy, uses, clearance of ingredients, etc.]
- Ensure application is complete, Form, 8570-1. In "me-too" applications, it is important to cite the name and registration number of the product claimed to be substantially similar to the pending product.
- Alternate formulation must be identified by a number or a letter in Box A of the CSF. Further, the reviewer needs only one copy of each new alternate CSF to guard against confusion since, in many situations, it is difficult to differentiate between them when there is a minor difference obscured among several ingredients.
- A Microsoft ® Excel worksheet has been placed on the Registration Division's website to aid submitters in calculating the correct nominal concentration.

[A] Product Chemistry Data:

1. Follow PR Notice 86-5 in organizing the submission.

2. Follow the specific requirements for each type of product whether it is EP or MP. Also, solubility in organic solvents is required along with solubility in water. Further, the storage stability and corrosion characteristics are required for all EPs and MPs (refer to Chapter V in the SOP http://www.epa.gov/oppfead1/guidance/product-sop.htm#_1_5). However, the Agency may grant "conditional registration" if the data is stated to be in progress. An accelerated stability study may be submitted for MP, but it does not exempt applicants from the one year storage stability requirement.

3. The GLP requirements are listed in 40CFR160. Some studies require full compliance, others partial, and the remaining no compliance (refer to chapter X of the SOP http://www.epa.gov/oppfead1/guidance/product-sop.htm#_1_17).

4. Include a Statement of Data Confidentiality and GLP/Quality Assurance Statements.

5. If the application for EP's/MPs that are formulated using registered sources, take advantage of PR Notice 98-1. The PR Notice explains the self-certification of product chemistry data process. The registrant need only submit four pages (a Statement of Data Confidentiality, GLP statement, Form 8570-36 (abstract summary of the physical/chemical properties), and Form 8570-37 (a self-certification statement) in lieu of a volume of information, Reference #7 in this document).

6. Remember that the data is reflected on the product's label and CSF so they should match. [Examples: the pH, density, and flammability cited in boxes 7, 8 & 9, respectively, of the CSF must be consistent with values in the submitted data. Also, the ingredient statement, substatements, the physical or chemical hazards statements, and storage and disposal statements in the label must be consistent with the data submitted. There must be a consistency between the label and CSF in citing the ingredient statement and whether the product is flammable or extremely flammable as shown in the data and box 9 of the CSF].

7. If registration is <u>not</u> requested for a new technical source, it must be supported with Groups A & B of product chemistry data. No need to submit a label or CSF.

8. For import tolerances, no need to submit a label or CSF, but supporting Groups A & B product chemistry data must be submitted along with a petition seeking tolerances for a product registered abroad. References must be made to the MRID's previously submitted when using a non-registered source that was approved by the EPA.

9. Production of a TGAI in a different facility and/or using different methods of manufacturing or different starting materials, must be supported with five batch analysis. This new TGAI can be claimed in an alternate CSF to a currently registered TGAI approved in a basic or alternate CSF. It can also be claimed in a current basic as an alternate source indicating the name and address of the producer and country where produced in boxes 1 & 6 of the CSF, along with those currently cited for the registered source.

10. The enforcement analytical method must be submitted/referenced for a new MP/TGAI. Copies of the method and samples of the product must be submitted to EPA's laboratory for validation. If applicable, the method can be referenced for a TGAI produced in a different facility or an EP/MP formulated using a registered TGAI source. Otherwise, a modified or a new method must be developed and submitted for review and validation by the EPA's laboratory. If using a non-registered source to formulate a product, reference the MRID number of that source citing the analytical method, or resubmit the method indicating it was previously submitted in MRID (number).

11. Helpful information can be found in Reference #10 when submitting an application to register a "me-too" product.

12. Table 1 below shows how to complete the label and CSF assuming a formulated product using 50 pounds from a non-registered TGAI, 96% pure containing impurity A at 2.4% and B at 1.6%: CSF (1) if the data on the TGAI was previously approved by the EPA, and CSF (2) if the data on the TGAI was not submitted, not reviewed, or found inadequate by the EPA. In situation 2, referral to HED will be necessary for their assessment as to the toxicological significance of carryover impurities, noting that the chemical name and CAS registry number of each impurity must be listed in column 10 of the CSF.

Table 1: Expressing values in pesticide labels and Confidential Statements of Formula (CSFs) when using non-registered technical sources in formulating products

Label	CSF (1)			CSF (2)		
	13(a) Lbs	13(b) %	15 Purpose	13(a) lbs	13(b) %	15 Purpose
Active Ingredient…… 48%	50	50 (48) (2)	Active Ing. Nominal Impurities	50	50 (48) (1.2) (0.8)	Active Ing. Nominal Impurity A Impurity B
Other Ingredients…… 52% Total…….. 100%	50	50	Inert Ing.	50	50	Inert Ing.

- **Note:** Nominal concentration = % w/w x TGAI purity [50% x 0.96%) = 48%. Also a Microsoft ® Excel worksheet has been placed on the Registration Division's website to aid submitters in calculating the correct nominal concentration.

[B] Product's Label:

Helpful guidance can be found in Chapter XI in the SOP (http://www.epa.gov/oppfead1/guidance/product-sop.htm#_1_18) entitled "Label Statements that Should be Reviewed by the Product Chemist."

Calculating the nominal concentration using the salt factor (Tip copied from #11, Chapter XI in the SOP):

Example: when cupric hydroxide reacts with naphthenic acid to form copper naphthenate), the nominal concentration of the salt complex that should be declared on the label can be calculated by multiplying the salt factor by the nominal concentration of free acid. The salt factor is calculated by dividing the molecular weight of copper naphthenate by that of naphthenic acid. The metallic equivalent is calculated by dividing the molecular weight of copper by the molecular weight of copper naphthenate X 100. This percentage should be indicated as a substatement to the ingredient statement.

This can be represented by the following equations:

$2C_5H_9COOH + Cu(OH)_2 \rightarrow CuC_5H_9(COOH)_2 + 2H_2O$

Naphthenic acid, MW = 113 + Cupric hydroxide → Copper naphthenate, MW = 287.55

Salt Factor = MW of Cu Naphthenate ÷ (2) MW of naphthenic acid = 287.55 ÷ (113 x 2) = 1.27

% of the PAI on the label = the nominal concentration of the free acid x 1.27 [the nominal concentration of Naphthenic acid = % w/w X its purity (from REFs)].

% Cu in the formulation = MW of Cu ÷ MW of complex x 100 = 63.55 ÷ 287.55 = 22.1%

Metallic Cu equivalent = % PAI on label x 0.221

[C] <u>The Confidential Statements of Formula (CSF)</u>:

Detailed information can be found in Chapter XII in the SOP, entitled "Review of the Confidential Statements of Formula (CSF)."

<u>Additional Tips by SRRD</u>:

1. Common errors found in the CSFs:

    a. The nominal concentration of the active ingredient is not calculated correctly.
    b. The certified limits on the active and inert ingredients are outside the allowable range presented in 40 CFR 158.175(b)(2) and the reason for the deviation is not provided (see item B below).
    c. The reviewer is not able to clear some inert ingredients that are mixtures because not enough information is provided.
    d. The reviewer is not able to cross check calculations of fertilizer ratios due to insufficient information on the fertilizer components of fertilizer-pesticide combination products (see D. 3 below).
    e. Missing Flash Point, pH, and Density data or the data sometimes do not match those from the submitted or referenced studies.

2. We will enforce the certified limits of active ingredients to comply with 40 CFR §158.175(b)(2) and (c). However, in some cases, we may accept a wider than allowed certified limits range if the registrant provides an acceptable justification and data that will support the proposed limits.

3. Although the Agency does not enforce the certified limits for inert ingredients, we are going to continue to address the deviations and request the registrant to comply with 40 CFR §158.175(b)(2). If the registrant does not comply, it will not be a ground for rejecting the CSF.

4. We are less concerned if the upper certified limit for an inert ingredient is off the allowable range. However, if the certified limit is zero, we will assume that the registrant is not using these inert ingredients in the formulation and they must submit an alternate formulation if these inerts are to be used, or clearly explain why "0.0" is a realistic lower certified limit.

5. In a formulation involving only one active ingredient and one inert, we will see to it

that the upper limit of the active ingredient and the lower limit of the inert, and vice versa, totals as close as possible to 100%.

6. If the certified limits are too broad and efficacy is a concern, we will ask the registrants to submit statements explaining their reasons, as well as encourage them to turn over data to justify why broader limits are used based on existing data for their formulation. It is also possible to ask the registrant to analyze the technical in order to document that the registrant's method detects the same percent active ingredient as the producer of the technical. If, after submission of additional data and analysis of the technical, we are still concerned, we will communicate with the CRM and PM in RD to explain our concern about efficacy, due to the registrant's difficulty in attaining the narrow certified limits.

[D] Other Topics:

1. How to Express Nominal Concentrations:

Refer to PR Notice 91-2 (Reference 6 in this document) and Chapter XIII in the SOP, entitled "How to Express Nominal Concentrations."

How to express the nominal concentration on the label and CSF of a formulated end-use product (a tip copied from Chapter XIII in the SOP (http://www.epa.gov/oppfead1/guidance/product-sop.htm#_1_20)

CSF: Source technical 96% pure

Column 13		Column 14	
(a) Amount in lbs	(b) % w/w	(a) % Upper Limit	(b) % Lower Limit
250 Active	25 (24)	(24.72)	(23.28)
350 Inert	35	36.05	33.95
400 Inert	40	41.2	38.8
1000	100		

Explanations to the Above Table and the Nominal Concentration/Percentage by Weight Concept:

If the label claim of nominal concentration is 24% and chemical purity of the TGAI is 96%, then by calculation, a formulator will use 250 pounds in a 1000-pound batch = 25% w/w [(250 ÷ 1000) X 100]. Material balance of 100% is achieved by adding two inerts totaling 750 pounds. To calculate the nominal concentration, multiply percentage by weight by chemical purity then divide by 100: [(25 X 96) ÷ 100] = 24%.

The general formula is: N = [(P X w/w) ÷ 100], where

N = nominal concentration
P = chemical purity of the TGAI
w/w = percentage by weight.

On the other hand, the percentage by weight can be calculated by dividing the label claim of nominal concentration by chemical purity then multiplying by 100: [(24 ÷ 96) X 100] = 25%.

Label

Active ingredient.....24%
Other Ingredients.....76%
Total…….....100%

2. Consistency Between the Label and CSF:

   Refer to Chapters XIV and chapter XV, entitled **"**Verify the Following to Guard Against Common Errors when Comparing the Label and CSF."

3. Identification of Fertilizers Components (tips by SRRD):

   - All fertilizer materials used in pesticide products, whether generated or premixed, must be identified on the CSF (per 40 CFR §158.155, 158.160 and 158.175). Registrants must list out the individual components of the fertilizer on the CSF, and must include N-P-K ratios, CAS numbers, chemical composition (% by weight), upper and lower certified limits and the name and address of the fertilizer source.

   - All possible variations in fertilizer components or alternate fertilizer materials used for a product must be presented on the CSF or in a separate confidential attachment to the CSF and must include the supplier's name and address.

   - In cases where a fertilizer product contain non-fertilizer components such as limestones, corn cobs, paraffin oil, etc, the non-fertilizer components must also be identified on the CSF and must include CAS numbers, % by weight and certified limits of each component.

References:

1. Code of Federal Regulations, Title 21.
2. Code of Federal Regulations, Title 40, Parts 158.150 to 158-190.
3. Code of Federal Regulations, Title 40, Parts 766.27.
4. Federal Register Notice: 49(207)FR42863,24/OCT/198.
5. OPPTS Test Guidelines, Series 830, Product Properties, EPA 712-C- 96, August, 1996.
6. PR Notice 91-2 Accuracy of stated percentages for ingredients statement.
7. Pesticide Regulations 98-1, entitled "Self-Certification of Product Chemistry Data."
8. Pesticide Registration (PR) Notice 98-10, "Notifications, Non-Notifications and Minor Formulation Amendments."
9. The Federal Insecticide, Fungicide, and Rodenticide ACT (FIFRA) and the Federal Food, Drug, and Cosmetic Act (FFDCA) As Amended by the Food Quality Protection Act (FQPA) of August 3,1996.
10. Malak, S. and D. McCall (2003). *Proposed Definitions, Specifications, and Data Requirements for Identical or Substantially Similar Pesticide Products*, Pesticide Formulations and Applications Systems: 23rd International Symposium, ASTM STP 1449, G. Volgas, R. Downer, and H. Lopez, eds., International, West Conshohocken, PA, pages 237-253.
11. Malak, S. and Betsy Grim (2003). *Standard Operating Procedure 2002-1 on Product Properties Data Requirements For Registration and Reregistration of Pesticides,* National Conference on Managing Environmental Quality Systems, Division on Information Quality Policies and Standards, New Orleans, Louisiana (54 pages). Internet Address: http://www.epa.gov/oppfead1/guidance/product-sop.htm