



Regulatory Directive

Chemistry Requirements for the Registration of a Technical Grade of Active Ingredient or an Integrated System Product

This Regulatory Directive details the chemistry requirements for registration under the *Pest Control Products Act* (PCPA) and Regulations and the recommended organization of Part 2 of the data submission. Guidance addressing the submittal of product-related analytical standards is also provided.

This document replaces Regulatory Directive Dir93-02, *Chemistry Requirements for the Registration of Technical Active Ingredients*, February 18, 1993. The revision process sought industry input through Regulatory Proposal Pro97-01, *Chemistry Requirements for the Registration of a Technical Grade of Active Ingredient or an Integrated System Product*, published in July 1997. Comments received were considered in the final version of the document.

The chemistry requirements have been harmonized with those of the U.S. Environmental Protection Agency (EPA) as described in the *Code of Federal Regulations* (CFR), 40 CFR § 158, and the *Product Properties Test Guidelines* 830 Series.

A tabular correlation between Pest Management Regulatory Agency (PMRA) and EPA guidance documents is provided in Appendix III to aid applicants in the compilation of a complete product chemistry package.

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Publications Coordinator
Pest Management Regulatory Agency
Health Canada
2250 Riverside Drive
A.L. 6606D1
Ottawa, Ontario
K1A 0K9

Internet: pmra_publications@hc-sc.gc.ca
www.hc-sc.gc.ca
Facsimile: (613) 736-3798
Information Service:
1-800-267-6315 or (613) 736-3799

Canada

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1.0 Introduction

Product chemistry information is developed and submitted for review in order to meet two objectives:

- (i) to identify and quantify the active ingredient(s) for purposes of the pest control product's certified limits; and
- (ii) to comprehensively characterize product composition, including active ingredient(s), impurities and formulants, in order to:
 - a) determine the uniqueness of each source of product with regard to purity and potency; and
 - b) assess the safety to humans and the environment in relation to the proposed use of the product.

The key requirement for meeting these objectives is the provision of detailed information on the composition of the technical grade of active ingredient (TGAI) or integrated system product (ISP), which is accomplished by submitting intensive analysis to 0.1% w/w with the determination of impurities of toxicological significance at any concentration¹. These data are to be accompanied by an explanation of methodology that, on its own merits, permits validation of procedures, results and conclusions. The analytical data must also be supported by a description of all starting materials² and the manufacturing process used to produce the pest control product.

Regulatory authorities must be able to assess the potential presence of impurities known to have, or suspected to have, health and/or environmental implications. The applicant should carefully consider the two objectives outlined above to ensure that the chemistry data generated will meet the Agency's requirements.

The PMRA has developed a series of Data Codes (DACOs) to address registration requirements on a use-site category (USC) basis. These are to be used as the basis for the chemistry package submission and will be screened for completeness prior to the review of the chemistry data. Complete instructions concerning the submission process are found in two Agency publications, Regulatory Proposals Pro96-01, *Management of Submissions Policy*, and Pro98-02, *Organizing and Formatting a Complete Submission for Pest Control Products*, both to be rewritten as Regulatory Directives.

¹ The appropriate level is dictated by the limit of quantitation (LOQ) of the toxic impurity analytical methodology, which is sample/chemical dependent, and must also be below any applicable regulatory limit.

² Any substance, including reactants, solvents and catalysts, used to manufacture or purify a pest control product.

Terminology and acronyms used throughout this document are defined in Appendix V and VI respectively. The use of the term *product* refers to both a TGAI and an ISP. The individual terms are specifically used where warranted.

2.0 Product Chemistry Data Requirements

Appendix I to this document identifies the data requirements for the registration of a TGAI or an ISP and includes additional guidance where warranted. A distinct Regulatory Directive, Dir98-03, identifies the chemistry requirements for manufacturing concentrates (MAs) and end-use products (EPs) derived from registered TGAI or ISPs. Since an ISP may be registered for manufacturing and/or end-use, the corresponding chemistry requirements identified in Dir98-03 must also be met if it is to be used directly as an EP.

Guideline Application

Please note that these data requirements may be partially or completely superseded by distinct guidance found in other PMRA publications, e.g., for specific pesticide types, including pheromones and microbial pest control agents as per the *Registration Handbook for Pest Control Products Under the Pest Control Products Act and Regulations*. If in doubt, it is recommended that the applicant confirm the relevance of these guidelines for a specific product with the Agency.

Requirements may be waived for some portions of the data requested in Appendix I, on a case-by-case basis, if the applicant can offer an acceptable written rationale based upon scientific reasoning. Such requests should appear in, or be referenced by the corresponding DACO number.

The PMRA may request additional data concerning any requirement found in this Regulatory Directive, also on a case-by-case basis, if deemed necessary for evaluation purposes.

3.0 Submittal Of Samples

Pursuant to the Pest Control Products Regulations, the Agency may request that product-related samples be provided by applicants. The PMRA's Laboratory Services maintains a central repository of all analytical standards submitted in response to the following requirements.

For new active ingredients and new sources of registered active ingredients, the following samples are required:

- (i) a 2.5-g analytical standard of the active ingredient, or if applicable, 1.0 g of each stereoisomer of an active ingredient. This refers to material that:

- a) has been purified and analysed extensively to give a certified purity of the active ingredient;
 - b) typically contains 95% or more of an active ingredient; and
 - c) may be used as an analytical standard to determine the purity of the same active ingredient in a pest control product or residues of the same active in/on foods or feeds or in the environment.
- (ii) a 1.0-g analytical standard of any impurity, metabolite or transformation product identified as a Residue of Concern (ROC). If any compounds are difficult or expensive to obtain, 100 to 200 mg may suffice. Standards are to include all ROCs identified by the applicant in response to data requirements found in Regulatory Directive Dir98-02, *Residue Chemistry Guidelines*, pending publication, as well as any additional ROCs identified by the Agency during the review process. The latter scenario is unlikely to occur if the applicant proceeds through the consultation phase as recommended in the *Residue Chemistry Guidelines*. ROC analytical standards refer to material that:
- a) has been purified and analysed extensively to give a certified purity of the ROC;
 - b) contains 95% or more of the ROC; and
 - c) may be used to determine the levels of the same ROC in pest control products or residues of the same compound in/on foods or feeds or in the environment.

If samples are unstable over a 2-year period, smaller amounts may be sufficient. Replacement samples may be requested after their expiry date.

The following samples may be required by the PMRA:

- (i) 10.0 g of the TGAI or ISP; and/or
- (ii) 1.0-g analytical standard of impurities in the TGAI or ISP and/or certain metabolites or degradation products. If any compounds are difficult or expensive to obtain, 100 to 200 mg may suffice.

Some or all of the above samples may be requested for active ingredients in products currently registered under the PCPA, e.g., for active ingredients under re-evaluation, or as required by the PMRA's Laboratory Services to maintain its inventory.

Samples are to be sent directly to:

Laboratory Services
Pest Management Regulatory Agency
Health Canada
Laboratory Services Building, No. 22
Central Experimental Farm
Ottawa, Ontario
K1A 0C6

NOTES:

- (1) Sample packaging must comply with the *Transportation of Dangerous Goods Act* and Regulations. Poorly packed, leaking, or otherwise damaged samples will be destroyed and replacement samples will be requested.
- (2) Samples must be properly labelled with concentration, weight and common or chemical names, not trade names or company codes.
- (3) A certificate or statement of purity including a description of the method used to determine purity must be provided with all analytical standards.
- (4) Storage instructions and information on shelf life (expiry date) must be provided for analytical standards. Material safety data sheets (MSDSs) must also be provided, if available.
- (5) Analytical standards of impurities must be labelled to include the common name of their associated TGAI or ISP.
- (6) Samples must be accompanied by correspondence indicating the reason for submission, e.g., requested by the PMRA as a requirement of registration, and include a corresponding submission number, if assigned, for ease of reference.
- (7) Unless accompanied by an MSDS, the acute oral and dermal toxicity of the sample should be supplied or at least be indicated on the sample label.

Data Requirements for Registration (Part 2 of Data Submission)

IDENTITY

Requirement: Identification information is required as described in Sections 2.1 to 2.10.

Purpose: To clearly identify the product, its active ingredient(s) and source of manufacture.

Guidance: Additional instructions are provided, as warranted, in each section.

2.1 Applicant's Name and Office Address

The *applicant* identifies the company that has the ultimate responsibility for certifying the information found on the PMRA Control Product Specification form (CPSF), as distinct from the *manufacturing plant*, which is addressed in Section 2.2 below.

2.2 Manufacturer's Name and Office Address and Manufacturing Plant's Name and Address

The actual *manufacturer* would typically form part of the same company identified in Section 2.1, above, but it could also reflect the use of a toll manufacturer. The *manufacturing plant* identifies the specific location at which the material is produced.

2.3 Product Trade Name

2.3.1 Other Names: Include any company development code as well as any equivalent foreign name to which data found in the submission may refer.

2.4 Common Name

Include the International Organization for Standardization (ISO) common name of each active ingredient or, if not as yet established, the proposed name.

2.5 Chemical Name

Both the International Union of Pure and Applied Chemistry (IUPAC) and Chemical Abstracts names of each active ingredient are to be provided. If applicable, each stereoisomer listed as an active ingredient must be individually identified and have a corresponding structure depicted in Section 2.7, below, showing the stereochemical designation(s).

2.6 Chemical Abstracts Service (CAS) Registry Number

Identify for each active ingredient or each isomer and/or group of isomers, if established.

2.7 Structural Formula

Provide for each active ingredient including, if applicable, each stereoisomer identified as an active ingredient.

2.8 Molecular Formula

2.9 Molecular Weight

2.10 [Reserved]

COMPOSITION

Requirement: Compositional data is required as described in Sections 2.11 to 2.13, below.

Purpose: To generate a comprehensive qualitative and quantitative listing of the ingredients that may be present in a product through knowledge of the starting materials used, the manufacturing process and assessment of the analytical methodology/data upon which the specifications are based. This information is used to support that the material can be consistently manufactured in accordance with the certified limits as expressed on the CPSF.

The Agency also uses composition data when reviewing new products to assess whether a TGAI or an ISP from a new source (manufacturer or manufacturing site), or produced by a new manufacturing method, is identical or substantially similar to any currently registered TGAI or ISP. This determines whether corresponding environmental, toxicological and/or value data with the Agency are relevant or whether new studies must be generated.

In addition, the data is used to ensure that the test material selected used to generate data supporting Parts 4-10 of the registration process is consistent with that identified on the CPSF.

Guidance: Additional instructions are provided below for each of Sections 2.11 to 2.13.

2.11 Manufacturing Methods

Information may be based upon pilot plant production or initial commercial production but must be updated to reflect current commercial production whenever applicable (see corresponding batch data requirement in clause 2.13.3).

2.11.1 Manufacturing Summary

Provide a brief overview of the manufacturing process outlining the major steps and reactants, summarizing the more comprehensive description required by clause 2.11.3 below. This is to include a general characterization of the process, e.g., batch or continuous, and the typical quantity of product produced per batch (or per unit time, if continuous).

2.11.2 Description of Starting Materials

The following information is to be provided for each starting material used to produce the active ingredient:

- (i) each brand name, trade name, common name, chemical name, CAS Registry number, or other commercial designation;
- (ii) the name and address of the companies that produce the starting materials or, if that information is not known to the applicant, the name and address of the companies that supply the starting materials; and
- (iii) all information concerning the composition of each starting material, including a copy of all specifications or other documents describing it.

It should be emphasized that an applicant is not required to perform chemical analysis of starting materials to meet the above criteria, but only provide information to which the applicant has, or should have, access.

The information required for formulants, if applicable to an ISP, is consistent with the three requirements identified above for starting materials.

If multiple suppliers are used for starting materials/formulants, specifications for all suppliers should be provided. Changes in suppliers once a product is registered are subject to the requirements of Regulatory Directive Dir94-01, *Notification/Non-Notification*, or subsequent revisions.

2.11.3 Detailed Production Process Description

An applicant must submit information on the manufacturing process used to produce the TGAI or ISP at each stage of production resulting in a separately isolated substance, as follows:

- (i) a flow chart of the chemical reactions, including structures, at each step of the process and of the major unit operations, including separation steps;

- (ii) the identities of the reactants, solvents and catalysts used to produce the product, their quantities and the order in which they are added;
- (iii) a description of the equipment used that may influence the composition of the substance produced;
- (iv) a description of the conditions, e.g., reaction time, temperature, pressure, pH, humidity, that are controlled during each step of the process to affect the composition of the substance produced, and the corresponding limits that are maintained;
- (v) a description of the purification steps, including those used to recover or recycle starting materials, intermediates or the substance produced; and
- (vi) a description of the procedures used to assure consistent composition of the substance produced, e.g., calibration of equipment, sampling regimens and other quality control measures such as tests used to monitor reaction completion.

Additional requirements are applicable to the manufacturing of stereoisomeric active ingredients. Three types of products may form during the manufacturing of such actives:

- (i) a racemic mixture;
- (ii) a single stereoisomer (enantiomer or diastereomer that, by definition, includes geometric [cis/trans or Z/E] isomers); or
- (iii) a stereoselectively enhanced isomeric mixture.

For (ii) and (iii), a full description of the stereoselective manufacturing process is to be provided. Stereospecific identity and purity is to be identified for starting materials.

2.11.4 Discussion of Formation of Impurities

The applicant must provide a discussion of the impurities that may be found in the product and why they may be present. The discussion should be based on established chemical theory and on what the applicant knows about the starting materials and the production process. The thoroughness of the theoretical discussion can be evaluated in parallel with the preliminary analysis data in Section 2.13, below, to assess whether potential impurities would be comprehensively identified by the methodologies used. If the applicant has reason to believe that an impurity the PMRA would consider to be toxicologically significant³ may be present, the discussion must include an expanded description of the

³ See Appendix I, clause 2.13.4, for a more detailed discussion of impurities of toxicological significance.

possible formation of the impurity and the amounts in which it might be present. The following potential sources of impurity formation must be discussed, as applicable:

- (i) each impurity that was found to be present in any analysis of samples produced according to the process identified in clause 2.11.3 conducted by or for the applicant; and
- (ii) each other impurity that the applicant has reason to believe *may be present* in a product at any time before use at a level \leq 0.1% by weight, based upon what is known about:
 - a) the composition (or composition range) of each starting material used to produce the product;
 - b) the impurities that are known to be present (or believed likely to be present) in the starting materials, and the known or presumed level (or range of levels) of these impurities;
 - c) the intended reactions and side reactions that may occur in the production of the product, and the relative amounts of byproduct impurities produced by such reactions;
 - d) the possible degradation of the ingredients in the product after its production but prior to its use;
 - e) the potential post-production reactions between the ingredients in the product;
 - f) the possible migration of components of packaging materials into the pest control product;
 - g) the potential carryover of contaminants from use of production equipment previously used to manufacture other products or substances; and
 - h) the process control, purification and quality control measures used to produce the product that may preclude the presence of potential impurities.

On a case-by-case basis, the PMRA may require an expanded discussion of potential impurity formation resulting from other potential chemical reactions, involving other ingredients, or at additional points in the production process.

2.12 Specifications

The nominal concentration and corresponding certified limits must be provided for each product component. The nominal concentration is defined as the typical amount of an ingredient present in a pest control product at the time of its production. Both the active ingredient nominal concentration and a corresponding nominal equivalence statement, if applicable, e.g., acid salts, are to be provided.

The product guarantee, identified on the CPSF and appearing on the draft product label, is synonymous with the active ingredient(s) nominal concentration. This number most accurately identifies the amount of active ingredient found in the TGAI or ISP and is subsequently used to establish corresponding enforceable certified limits, as further discussed in clause 2.12.1 below.

Precise identification of impurities present in products at or above 0.1% by weight is required while the components of toxicological concern must be identified at any concentration⁴. The composition of a minimum of five batches of the product, determined using specific methods and universal detectors, must be provided to support the specifications, as further described in Appendix I, clause 2.13.3. The submission is to include the structural formulae of all specified impurities.

Required (R) and conditionally required (CR) data for the active ingredient(s) and other product components are to be submitted according to the following table:

⁴ The appropriate level is dictated by the limit of quantitation (LOQ) of the toxic impurity analytical methodology, which is sample/chemical dependent, and must also be below any applicable regulatory limit.

Table 1: Product Component Identification

TGAI or ISP Component	Common (or Trade ⁵) Name	CAS Chemical Name	CAS No.	Component % by Weight (nominal guarantee)	Lower Certified Limit	Upper Certified Limit	Purpose In Product
Active ingredient(s)	R	R	R	R	R	R	R
Formulants (if applicable to an ISP)	R	R	R	R	R	R	R
Impurities of toxicological significance associated with the active ingredient (at any concentration ⁴)	CR ⁶	R	CR ⁶	R		R	Identify as an impurity
Other impurities associated with the active ingredient at \$0.1%	CR ⁶	R	CR ⁶	R		R	Identify as an impurity

Specifications for the TGAI or ISP are to include stereoselective tests for the identity and purity of stereoisomers. Distinct, suitably validated methodology⁷ is typically required to establish enantiomeric purity. For all types of stereoisomer mixtures, specified limits are required for each active component. A reference standard of high stereochemical purity should be available for each specified stereoisomer and ideally, reference standards should be available for all other potential stereoisomeric impurities. Limits are to be specified for individual stereoisomeric impurities, as supported by preliminary batch analysis as described in clause 2.13.3, below. The stability of the optically pure/enhanced active ingredient(s) towards chiral inversion or other isomerization is to be investigated and reported as per clause 2.14.13 or 2.14.14, below, as applicable.

2.12.1 Establishing Certified Limits

Standard certified limits for active ingredients and formulants are based upon nominal concentration, unless an applicant proposes, and justifies, alternate limits which are deemed acceptable by the PMRA. The applicant must propose upper certified limits for impurities as standard certified limits may not be used for such components.

Standard limits are defined in the following table:

⁵ Include only if a common name is unavailable, such as for certain formulant mixtures.

⁶ To be provided if established.

⁷ For example, High-Performance Liquid Chromatography, Gas Chromatography, or Capillary Electrophoresis systems capable of resolving chiral substances; or structural conversion to diastereomers.

Table 2: Standard Certified Limits

Nominal Concentration of Ingredient	Upper Limit	Lower Limit
20.0% < N # 100.0%	N + 3% N	N - 3% N
1.0% < N # 20.0%	N + 5% N	N - 5% N
N # 1.0%	N + 10% N	N - 10% N

An applicant may propose a certified limit for an active ingredient or formulant that differs from the standard limits, but must include an explanation of the basis for the proposed limits, including how they were established, e.g., sample analysis or a quantitative estimate based upon the production process. Proposed limits should not greatly exceed those actually occurring in the product.

All certified limits must:

- (i) be based on a consideration of the variability of the concentration of the ingredient in the product when good manufacturing practices and normal quality control procedures are used;
- (ii) allow for all sources of variability likely to be encountered in the production process; and
- (iii) take into account the stability of the ingredient in the product and the possible formation of impurities between production and sale or distribution.

If the PMRA finds any certified limit unacceptable (either standard or applicant proposed), the Agency will inform the applicant of its determination and will provide supporting reasons. The PMRA may also require, on a case-by-case basis, any or all of the following:

- (i) more precise limits;
- (ii) a more thorough explanation of how the certified limits were determined; or
- (iii) a narrower range between the upper and lower certified limits than that proposed.

2.12.2 Control Product Specification Form

Specification data are to be submitted on a CPSF that includes a signed and dated *Declaration of Applicant* certifying that the information is true and complete.

Full instructions on the proper completion of the form are included with the CPSF.

2.13 Preliminary Analysis

2.13.1 Methodology/Validation

Methodology for specifically identifying and quantifying the active ingredient(s) and impurities present in products at or above 0.1% by weight, or those of toxicological significance at any concentration⁸, is to be provided. A more thorough discussion of impurities of toxicological significance is provided in clause 2.13.4, below; however, all corresponding analytical methodology is to be reported under this DACO number.

A method capable of separating stereoisomers, when applicable, as identified in Section 2.12, above, is also required and may result in the need for two methods for the active ingredient(s); one for total stereoisomeric content and a second to confirm any specified ratio.

The recommended reporting format for analytical methodology is outlined in Appendix II.

All methodology must have sufficient precision and accuracy to determine whether the amount of the ingredient found in any sample of the product is within its certified limits.

2.13.2 Confirmation of Identity

The identity of the active ingredient and each specified impurity must be supported by relevant chromatograms and/or spectra. Ideally, full spectral characterization by mass spectrometry (MS) of each isolated impurity (or on-line determination using gas chromatography/MS or liquid chromatography/MS) by comparison to the spectrum of a corresponding analytical standard is required. However, if an impurity is expected due to its presence in a starting material or formation as a reaction intermediate in the manufacturing process, as discussed by the applicant in clause 2.11.4, above, chromatographic retention time comparison to a corresponding analytical standard, whose identity and structure has been confirmed, is acceptable to support its identity.

2.13.3 Batch Data

The composition of a minimum of five batches of the product, determined using specific methods and universal detectors, must be provided to support the specifications. Corresponding raw data to be submitted includes representative quantitative chromatograms of: (1) standards; and (2) the five batches of the TGAI or ISP that were used to support each specified active ingredient and impurity. Chromatograms must be

⁸ The appropriate level is dictated by the limit of quantitation (LOQ) of the toxic impurity analytical methodology, which is sample/chemical dependent, and must also be below any established applicable regulatory limit.

clearly labelled to identify all analytical parameters and peaks, including those that may represent compounds quantitated by other methods included in the submission.

These samples may represent pilot plant production; however, if production is scaled up at the same location or if a distinct facility/process is used for commercial manufacturing, data from an additional five batches, corresponding to the current location/process, are required to support the specifications.

2.13.4 Impurities of Toxicological Concern

Analysis for these impurities is required when there is a potential for their presence in starting materials or their formation during the manufacture of the technical active ingredient.

For example, nitrosamine analysis is required when appropriate amines and an identifiable nitrosating agent (including nitrites and nitrates) are present due to the raw materials or manufacturing process utilized. The primary focus is upon smaller molecular weight volatile and nonvolatile nitrosamines, such as N-dimethylnitrosamine (NDMA) and N-nitrosodipropylamine (NDPA) respectively, rather than larger molecules such as nitrosoglyphosate or nitrosoureas. It should be noted that inherent contamination would be expected from products whose chemical structure features both amine functionality and nitrosating potential, such as dinitroanilines.

These analyses, when required, should reflect the lowest practical limit of quantitation (LOQ), which will vary according to the sample and chemical, but must at least be below any corresponding applicable regulatory level. Upper certified limits are required for impurities of toxicological significance present above the LOQ.

Any waiver request for not providing such data must be supported by scientific rationale as to why the presence of such impurities can be excluded and will be assessed based upon the nature of the raw materials, chemistry of the active ingredient and the specific manufacturing process.

Impurities and classes of impurities of toxicological concern include, but are not limited to:

- 2,3,7,8-tetrachloroazobenzene (TCAB) and 2,3,7,8-tetrachlorooxybenzene (TCAOB)
- Anilines and substituted anilines
- Dichloro diphenyl trichloroethane (DDT) and other chlorinated diphenyl ethanes and ethylenes, such as analogs and isomers of DDT, DDD, DDE and Cl-DDT (extrachloro DDT)
- Ethylene thiourea (ETU)
- Halogenated dibenzodioxins/halogenated dibenzofurans

-
- Hexachlorobenzene (HCB)
 - Hydrazines
 - Nitrosamines
 - Oxygen analogs of organophosphates
 - Polynuclear aromatics (PNAs) also referred to as polynuclear aromatic hydrocarbons (PAHs)
 - Polychlorinated biphenyls (PCBs)
 - Sulfoxides and sulfones of organophosphates and carbamates
 - Tetraethyl thiodiphosphate (Sulfotep) or tetraethyl pyrophosphate (TEPP)

Impurities having characteristics of potential toxicological significance may include:

- (i) any impurity that is a structurally related analog of the parent compound of toxicological significance;
- (ii) any impurity that is also an active ingredient; or
- (iii) any impurity that is identified in standard toxicology data bases, such as Toxline or the Registry of Toxic Effects of Chemical Substances (RTECS), as being oncogenic, neurotoxic, genotoxic, or a developmental toxicant, endocrine disrupter, etc.

If a product has been analysed for any of these compounds, methodologies, validation data including recovery and Limit of Detection (LOD)/LOQ for expected contaminant(s), or reasonable surrogates if appropriate, and batch data as per clause 2.13.3, are to be provided. Where it is deemed essential for evaluation, such data from pest control products or potential precursors will be requested. Since detection and quantitation limits may vary from case to case, consultation with the PMRA is recommended.

Applicants should contact the Agency's Health Evaluation Division if there is a question about the status of any specific impurity not listed.

PROPERTIES

Requirement: To provide methodology and observations/values for the properties identified below in 2.14.1 to 2.14.14.

Purpose: Property data are requested for a number of reasons. The requirements include properties that:

- (i) are used directly in risk assessment as they represent one of a number of factors that influence concentration and exposure. Certain properties are indicators of the behaviour of a pesticide in the environment with respect to mobility and accumulation;

- (ii) are needed as basic or supportive evidence in initiating or evaluating studies required by other disciplines. For example, the octanol/water partition coefficient is used as a criterion in determining whether certain bioaccumulation/bioconcentration studies must be conducted and UV/visible absorption identifies wavelengths of light at which compounds may be susceptible to phototransformation;
- (iii) confirm or provide supportive information on the identity of ingredients and products;
- (iv) provide information that is useful in reviewing the manufacturing process used to produce the pest control product as well as the methodologies used for its analysis; and/or
- (v) permit response to emergency requests for identification of unlabelled pest control products potentially involved in accidents, spills, or medical emergencies such as poisonings.

Guidance: Protocols for developing the data requirements identified in this section are not included in this document. Applicants should consult protocols developed and published by various agencies, including those referenced in the comparative table below or listed in Appendix IV.

2.14 Chemical and Physical Properties

Property data requirements are identified in Table 3.

Methodology must be thoroughly described or a copy of the scientific publication describing the protocol must be included with the submission. A reference to internationally established protocols is sufficient, if followed without deviation, and the specific procedure used is clearly identified for those protocols providing multiple options. Study reports should include a complete presentation of the data, sample calculations and an interpretation of the results. In addition, basic physio-chemical information on individual stereoisomers is to be provided, if applicable; typically, this may include information on melting point, optical rotation, and stability towards inversion. A pure active ingredient (PAI) is equivalent to the analytical standard of active ingredient described under Section 3.0.

Care should be exercised in the selection of appropriate test materials for properties that provide a TGAI or PAI option to ensure data relevance. Typically, as these properties are characteristic of the active principle, the PAI should be used whenever available. This is most important for properties that may be significantly affected by impurities, such as water solubility, particularly in the presence of residual solvents. Conversely, it may be appropriate to use the TGAI if impurities do not significantly

impact upon the outcome of the test and if the corresponding detection principle is selective for the PAI. For example, certain vapour pressure protocols may be conducted on either the TGAI or PAI. Regardless of the material used, the purity of the test substance must always be clearly identified in the study report.

Table 3: Chemical and Physical Properties

Clause	Property	Test Substance	Property Notes	Ag Can ⁹ T-1-255	EPA (830 Series)	OECD ¹⁰
2.14.1	Colour	TGAI ¹¹			830.6302	
2.14.2	Physical state	TGAI ¹¹			830.6303	
2.14.3	Odour	TGAI ¹¹			830.6304	
2.14.4	Melting point/melting range	TGAI ¹¹ or PAI	1		830.7200	102
2.14.5	Boiling point/boiling range	TGAI ¹¹ or PAI	2		830.7220	103
2.14.6	Density or specific gravity	TGAI ¹¹	3		830.7300	109
2.14.7	Water solubility (mg/L)	TGAI ¹¹ or PAI	4	T	830.7840 830.7860	105
2.14.8	Solvent solubility (mg/L)	TGAI ¹¹ or PAI	5		830.1000	
2.14.9	Vapour pressure	TGAI ¹¹ or PAI	6	T	830.7950	104
2.14.10	Dissociation constant	TGAI ¹¹ or PAI	7		830.7370	112
2.14.11	Octanol/water partition coefficient	TGAI ¹¹ or PAI	8	T	830.7550 830.7560 830.7570	107 117
2.14.12	UV/visible absorption spectra	TGAI ¹¹ or PAI	9		830.7050	101
2.14.13	Stability (temperature, metals)	TGAI	10,12, 13		830.6313	113
2.14.14	Storage stability data	ISP	11, 12		830.6317	

PROPERTY NOTES:

- General: (i) Several of the identified tests require the use of distilled water. Although double distilled water is preferred, deionized water with a resistivity greater than 10 megohms/cm and a total organic content below 0.01% is also acceptable.
- (ii) If data are not required for a specific property of a product, as per the notes, include this information in the corresponding section of the submission.

- (1) Required when the test substance is a solid at room temperature.
- (2) Required when the test substance is a liquid at room temperature.

⁹ Agriculture Canada, *Guidelines for Determining Environmental Chemistry and Fate of Pesticides*, Trade Memorandum T-1-255, 1987.

¹⁰ OECD: Organisation for Economic Co-operation and Development

¹¹ If the TGAI cannot be isolated, i.e., for an ISP, these data are required on the practical equivalent of the TGAI.

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- (3) Bulk density must be defined for solids. True density or specific gravity are applicable to other test substances.
 - (4) Solubility in water may be a function of pH if the compound ionizes in an aqueous solution. In such situations, it may be necessary to determine solubility at more than a single pH (see EPA 830.7860, *Effect of pH on solubility*).
 - (5) Required in representative polar and non-polar solvents at $20^{\circ} \pm 5^{\circ}\text{C}$.
 - (6) Required unless the substance is a salt. For methodologies requiring the use of elevated temperatures, the vapour pressure should not be extrapolated over a phase change unless $\log p$ (pressure) versus $1/T$ (temperature) linearity is maintained.
 - (7) Required when the test substance contains an acid or base functionality. For products that are salts, data are required for the corresponding acid/base.
 - (8) Determined at pH 5, 7 and 9 for all organic chemicals unless they hydrolyse in water or are soluble in water in all proportions.
 - (9) Not required in the absence of a UV chromophore. Absorption at wavelengths between 300 and 900 nm are of particular interest in assessing the potential for photodegradation. Where it is not possible to obtain sufficient concentrations in aqueous media, a suitable organic solvent should be used, with methanol preferred. Further guidance in the performance of the test are found in the referenced EPA and Organisation for Economic Co-operation and Development (OECD) guidance documents.
 - (10) Data regarding stability to metal and metal ions is required only if contact with metals during storage or use is likely.
 - (11) Storage stability data must adhere to the following requirements:
 - (i) Samples of the material must be stored for at least one year at a constant ambient temperature or under warehouse conditions that reflect the expected storage conditions of the commercial product.
 - (ii) The study shall be conducted with the product in its commercial package or in smaller packages of the same construction and materials. If the package is permeable, a relative humidity of at least 50% must be maintained throughout the study.
 - (iii) The study should be carried out with sufficient replicates and sufficient sampling frequency to establish the actual shelf-life if degradation occurs within one year. If a product has a shelf life of less than one year, an expiration date may be required on the product container.

- (iv) The analysis is to be conducted by a specific method, normally following the same protocol used to assess the level of active ingredient in response to clause 2.13.1 of this Appendix. However, if the methodology differs, it must be fully described as per Appendix II.
- (v) The storage stability report submitted in support of registration shall include the following information:
 - (a) a description of test procedures and conditions, e.g., study duration and temperature;
 - (b) a description of any physical changes, e.g., phase separation or clumping and any changes to the integrity of the packaging during the test period; and also of the consequences, if any, of such changes for safe handling and use of the product; and
 - (c) quantitative analytical data for the active ingredient at study commencement and following storage periods of 3, 6 and 12 months.
- (12) The protocol must include a test to monitor for the stability of optically pure/enhanced active ingredient(s) towards chiral inversion or other isomerization, if applicable, as per Section 2.12.
- (13) The temperature stability requirements for a TGAI, as per the referenced guidance documents, reflect Collaborative International Pesticides Analytical Council (CIPAC) MT 46 methodology, i.e., 14 days at 54°C. Methodology for the analysis of the active ingredient(s) would typically be consistent with that provided in clause 2.13.1; however, if the methodology differs, it must be fully described as per Appendix II.

Analytical Data Reporting Format

This Appendix is included primarily to address the issue of content and to suggest a consistent format for ease of data review; however, it is the content that is of primary significance and a report need not be rewritten to adapt to the format suggested.

Preliminary pages

Title/cover page

Table of Contents

Introduction and Summary

Scope	Identify the analyte(s) for which the method has been validated.
Source of method	Include a reference to a published method, such as sources listed in Appendix IV, if applicable.
Analytical principles	Provide a brief description, including the identification of the chemical species determined, the range over which the analyte(s) has (have) been analysed and, for impurities, the limits of detection and sensitivity.

Materials and Methods

Equipment	List and describe.
Reagents and standards	List and describe source and preparation.
Analytical procedure	Detail in a stepwise fashion, with special emphasis on reagents or procedural steps requiring special precautions to avoid safety or health hazards, including: <ul style="list-style-type: none">(i) preparation of sample;(ii) extraction (if any);(iii) clean-up (if any);(iv) derivatization (if any); and(v) instrumental analysis, including:<ul style="list-style-type: none">a) description - make/model, type/specificity of detectors, columns, packing materials, carrier gases, mobile phase, etc.;b) operating conditions - flow rates, detector wavelength, temperatures, voltage, etc.; and

c) calibration procedures.

Methods of calculation	Describe in a stepwise fashion.
Other	Identify any and all relevant information the applicant considers appropriate to provide a complete and thorough description of the analytical methodology and the means of calculating the results, i.e., critical control points.

Results and discussion

Describe the established performance criteria for the method.

Accuracy

Precision Identify the number of replicates used.

LOD/LOQ Provide definition used

Selectivity/specificity Describe tests used to establish the lack of interferences from other product components or from solvents and materials used in the methodology.

Ruggedness testing If performed.

Limitations

Linear range

Tables and figures

These are to be fully referenced to the body of the report and included where appropriate.

References

Appendices

Representative chromatograms, spectra, etc.	As applicable and in accordance with Section 2.13 of this appendix.
Other	Any relevant material not fitting into any other sections of this report.

Table 4: Correlation of Corresponding PMRA/EPA Guidance Documents

PMRA Regulatory Directive Dir98-04		Corresponding EPA Documentation		
Section	Section Title	EPA No.	EPA Title ¹²	40 CFR 158
1.0	Introduction	830.1000	Background for Product Properties Test Guidelines	
2.0	Product Chemistry Data Requirements	830.1000	Background for Product Properties Test Guidelines	
3.0	Submittal of Samples	830.1900 860.1650	Submittal of Samples Submittal of Analytical Reference Standards	158.190 158.240
Appendix 1	Data Requirements for Registration (Part 2 of Data Submission)			
2.1	Applicant's Name and Office Address			
2.2	Manufacturer's Name and Office Address and Manufacturing Plant's Name and Address			
2.3	Product Trade Name	830.1000	Background for Product Properties Test Guidelines	
	2.3.1 Other Names	830.1000	Background for Product Properties Test Guidelines	
2.4	Common Name	830.1550	Product Identity and Composition	158.155
2.5	Chemical Name	830.1550	Product Identity and Composition	158.155
2.6	Chemical Abstracts Registry Number	830.1550	Product Identity and Composition	158.155
2.7	Structural Formula	830.1550	Product Identity and Composition	158.155
2.8	Molecular Formula	830.1550	Product Identity and Composition	158.155
2.9	Molecular Weight	830.1550	Product Identity and Composition	158.155
2.10	[Reserved]			
2.11	Manufacturing Methods			
	2.11.1 Manufacturing Summary	830.1620	Description of Production Process	158.162
	2.11.2 Description of Starting Materials	830.1600	Description of Materials Used to Produce the Product	158.160
	2.11.3 Detailed Production Process Description	830.1620	Description of Production Process	158.162
	2.11.4 Discussion of Formation of Impurities	830.1670	Discussion of Formation of Impurities	158.167
2.12	Specifications	830.1550	Product Identity and Composition	158.155
	2.12.1 Establishing Certified Limits	830.1750	Certified Limits	158.175
	2.12.2 Control Product Specification Form	830.1550	Product Identity and Composition (Confidential Statement of Formula)	158.155
2.13	Preliminary Analysis			
	2.13.1 Methodology / Validation	830.1700	Preliminary Analysis	158.170
	2.13.2 Confirmation of Identity	830.1700	Preliminary Analysis	158.170
	2.13.3 Batch Data	830.1000 830.1700	Background for Product Properties Test Guidelines Preliminary Analysis	158.170

¹² The EPA 830 Series of requirements supersede the 1982 *Pesticide Assessment Guidelines Subdivision D, Product Chemistry*.

	2.13.4 Impurities of Toxicological Concern	830.1700	Preliminary Analysis	158.170
2.14	Chemical and Physical Properties	Various	See Correlation in Appendix I, Section 2.14	158.190

References for Developing Chemistry Data

Applicants should ensure that they have the latest editions of the following documents.

1. Agriculture Canada, *Guidelines for Determining Environmental Chemistry and Fate of Pesticides*, Trade Memorandum T-1-255, 1987.
2. American Society for Testing and Materials, *Annual Book of ASTM Standards*; ASTM, Philadelphia, PA, U.S.
3. Association of Official Analytical Chemists, *Official Methods of Analysis of AOAC- International*; AOAC-International, Arlington, VA, U.S.
4. Collaborative International Pesticide Analytical Council, *CIPAC Handbooks*, CIPAC, Hatching Green, Harpenden, Hertfordshire, England, 1970 - 1995.
5. Organisation for Economic Co-operation and Development, *Guidelines for Testing of Chemicals*, OECD 101 - 117; OECD, Paris, France, 1981 - 1995.
6. United States Environmental Protection Agency, *Product Properties Test Guidelines (830 Series)*; U.S. Government Printing Office, Washington, DC, U.S., 1996.
7. United States Environmental Protection Agency, *EPA Manual of Chemical Methods for Pesticides and Devices*, 2nd edition; AOAC, Arlington, VA, U.S., 1992.

Definition of Terminology

Note: Italicized text found in a definition identifies that the term is also defined in this appendix.

Active ingredient: the ingredient(s) of a control product to which the effects of the pest control product are attributed, including a synergist, but does not include a solvent, diluent, emulsifier or component that by itself is not primarily responsible for the control effect of the product.

Diastereomer: *stereoisomers* not related as mirror images

Enantiomer: one of a pair of molecular species that are non-superimposable mirror images of each other.

End-use product: a product containing *active ingredient(s)* and usually *formulant(s)* that is labelled with instructions for direct pest control use or application.

Formulant: any substance or group of substances other than an *active ingredient* that is intentionally added to a pest control product to improve its physical characteristics, e.g., sprayability, solubility, spreadability, and stability.

Guarantee: the typical or *nominal concentration* of an ingredient that is expected to be present in a representative sample of a pest control product at the time of its production.

Impurity: any substance in a control product other than an *active ingredient* or a *formulant*, e.g., contaminants, residual starting materials, reaction products, degradation products or products added for purposes of extraction or purification.

Integrated system product: may be used in manufacture of an *end-use product* or may itself be an *end-use product*; formed in a manufacturing process in which the ISP

- (a) contains an *active ingredient* that is not isolated due to physical limitations or uncertainty as to the specific active component(s); or
- (b) is purposely left as a mixture of components due to manufacturing or integrity considerations.

Isomers: chemical species with identical molecular formulae that differ in atomic connectivity (including bond multiplicity) or spatial arrangement.

Manufacturing concentrate: a product containing a registered *technical grade of active ingredient(s)* and *formulant(s)* intended for further reformulating and/or repackaging into *end-use products*.

Nominal concentration: the typical amount, or *guarantee*, of an ingredient that is expected to be present in a representative sample of a pest control product at the time of its production.

Residue of concern: describes the sum of the parent pesticide and its degradation products, metabolites, *impurities* and *formulants* (as applicable) that are of toxicological concern. In addition, those residues which represent greater than 10% of the terminal radiolabelled residue are included in the ROC.

Starting material: any substance, including reactants, solvents and catalysts, used to manufacture or purify a pest control product.

Stereoisomers: *isomers* with identical atomic connectivities and differing only by the spatial arrangements of their atoms or groups. Subclasses are *enantiomers* and *diastereomers*.

Technical active ingredient: see *technical grade of active ingredient*.

Technical grade of active ingredient: contains the *active ingredient* and normally contains *impurities* that are by-products of the manufacturing process

Acronym List

C1-DDT	Extrachloro DDT
CAS	Chemical Abstracts Service
CFR	Code of Federal Regulations
CIPAC	Collaborative International Pesticides Analytical Council
CPSF	Control Product Specification Form (PMRA)
CR	Conditionally Required
CV	Coefficient of Variation
DACO	Data Code
DDD	Dichloro diphenyl dichloroethane (also known as TDE)
DDE	Dichloro diphenyl dichloroethylene
DDT	Dichloro diphenyl trichloroethane
EPA	Environmental Protection Agency (U.S.)
EP	End-Use Product
ETU	Ethylene thiourea
FIFRA	Federal Insecticide, Fungicide and Rodenticide Act (EPA)
HCB	Hexachlorobenzene
ISO	International Organization for Standardization
ISP	Integrated System Product
IUPAC	International Union of Pure and Applied Chemistry
LOD	Limit of Detection
LOQ	Limit of Quantitation
MA	Manufacturing Concentrate
MS	Mass Spectrometry
MSDS	Material Safety Data Sheet
OECD	Organisation for Economic Co-operation and Development
PAH	Polynuclear aromatic hydrocarbon
PAI	Pure Active Ingredient
PCB	Polychlorinated biphenyl
PCPA	Pest Control Products Act
PMRA	Pest Management Regulatory Agency
PNA	Polynuclear aromatics
R	Required
ROC	Residue of Concern
RTECS	Registry of Toxic Effects of Chemical Substances
TCAB	2,3,7,8-tetrachloroazobenzene
TCAOB	2,3,7,8-tetrachloroazuoxybenzene
TEPP	Tetraethyl pyrophosphate
TGAI	Technical Grade of Active Ingredient
USC	Use-Site Category