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Directorate-General for Agriculture

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GUIDELINE DEVELOPED WITHIN THE STANDING COMMITTEE ON PLANT HEALTH WITH
REGARD TO THE
APPLICABILITY OF GOOD LABORATORY PRACTICE TO DATA REQUIREMENTS ACCORDING TO
ANNEXES II, PART A, AND III, PART A, OF COUNCIL DIRECTIVE 91/414/EEC

INTRODUCTION

1. If GLP is mentioned in the first column all tests and analyses have to be performed in accordance with the principles laid down in Council Directive 87/18/EEC. This implies also where relevant the requirements defined in the OECD GLP Consensus Documents "THE APPLICATION OF THE GLP PRINCIPLES TO SHORT-TERM STUDIES", ENVIRONMENT MONOGRAPH NO. 73, 1993, and "THE APPLICATION OF THE PRINCIPLES OF GOOD LABORATORY PRACTICE TO FIELD STUDIES".
2. Where in the first column GLP* is mentioned the derogations of paragraph 2.2 of the introduction to Annex II and of paragraph 2.4 of Annex III of Council Directive 91/414/EEC, amended by Commission Directive 93/71/EEC and Commission Directive 95/35/EEC, apply.
3. For section 6 of Annex III (Efficacy) the provisions of points 2.2 and 2.3 of the introduction to Annex III of Council Directive 91/414/EEC, as amended by Commission Directive 93/71/EEC apply.

Generally the provisions of GLP have to be applied only where experimental data are generated.

This document gives guidance to the Member States in their requirements to applicants performing studies required under Council Directive 91/414/EEC.

ANNEX II

	1.1	<u>Applicant (name, address, etc.)</u>
	1.2	<u>Manufacturer (name, address, including location of</u>
	1.3	<u>Common name proposed or ISO-accepted, and synonyms</u>
	1.4	<u>Chemical name (IUPAC and CA nomenclature)</u>
	1.5	<u>Manufacturer's development code number(s)</u>
	1.6	<u>CAS, EEC and CIPAC numbers (if available)</u>
	1.7	<u>Molecular and structural formula, molecular mass</u>
	1.8	<u>Method of manufacture (synthesis pathway) of the active</u> <u>e</u>
	1.9	<u>Specification of purity of the active substance in g/kg</u>
	1.10	<u>Identity of isomers, impurities and additives (e.g.</u> <u>ers), together with the structural formula and the content</u> <u>d as g/kg</u>
GLP	1.11	<u>Analytical profile of batches</u>
	2.1	----- <u>Melting point and boiling point</u>
GLP	2.1.1	<u>Melting point</u>
GLP	2.1.2	<u>Boiling point</u>
GLP	2.1.3	<u>The temperature of decomposition or sublimation</u>
GLP	2.2	<u>Relative density</u>
	2.3	<u>Vapour pressure (in Pa), volatility (e.g.</u> <u>law constant)</u>
GLP	2.3.1	<u>Vapour pressure</u>
GLP	2.3.2	<u>Volatility</u>
	2.4	<u>Appearance (physical state, colour and odour;</u> <u>)</u>
	2.4.1	<u>Colour and physical state</u>
	2.4.2	<u>Odour</u>
	2.5	<u>Spectra (UV/VIS, IR, NMR, MS), molecular</u> <u>on at relevant wavelengths</u>
GLP	2.5.1	<u>Spectra of active substance</u>
GLP	2.5.2	<u>Spectra of impurities</u>
GLP	2.6	<u>Solubility in water including effect of pH (4 to</u> <u>olubility</u>
	2.7	<u>Solubility in organic solvents</u>
GLP	2.8	<u>Partition coefficient n-octanol/water including</u> <u>f pH (4 to 10)</u>
	2.9	<u>Stability in water, hydrolysis rate,</u> <u>nical degradation, quantum yield and identity of breakdown</u> <u>s), dissociation constant including effect of pH (4 to 9)</u>
GLP	2.9.1	<u>Hydrolysis rate</u>
GLP	2.9.2	<u>Direct phototransformation</u>
GLP	2.9.3	<u>Quantum yield of direct photodegradation in</u>
GLP	2.9.4	<u>Dissociation constant(s) (pKa values)</u>
GLP	2.10	<u>Stability in, air, photochemical degradation,</u> <u>reakdown product(s)</u>

	2.11	<u>Flammability including auto-flammability</u>
GLP	2.11.1	<u>Flammability</u>
GLP	2.11.2	<u>Auto-flammability</u>
GLP	2.12	<u>Flash point</u>
GLP	2.13	<u>Explosive properties</u>
GLP	2.14	<u>Surface tension</u>
GLP	2.15	<u>Oxidizing properties</u>

		<u>Function, e.g. fungicide, herbicide, insecticide, with regulator</u>
	3.2	<u>Effects on harmful organisms, e.g. contact poison, stomach poison, fungitoxic or fungistatic, etc., systemic effects</u>
	3.3	<u>Field of use envisaged, e.g. field, protected of plant products, home gardening</u>
	3.4	<u>Harmful organisms controlled and crops or products created</u>
	3.5	<u>Mode of action</u>
	3.6	<u>Information on the occurrence or possible the development of resistance and appropriate management</u>
	3.7	<u>Recommended methods and precautions concerning storage, transport or fire</u>
	3.8	<u>Procedures for destruction or decontamination</u>
	3.8.1	<u>Controlled incineration</u>
GLP	3.8.2	<u>Others</u>
	3.9	<u>Emergency measures in case of an accident</u>

		<u>methods for the determination of pure active substance and, where appropriate, for relevant breakdown products, isomers and impurities of the active substance and additives (e.g. stabilizers) in the active substance</u>
		<u>manufactured</u>
	4.2	<u>Analytical methods including recovery rates and the determination for the</u>
		<u>determination of residues</u>
	4.2.1	<u>Residues in plants, plant products, foodstuffs,</u>
	4.2.2	<u>Residues in soil</u>
	4.2.3	<u>Residues in water (including drinking water)</u>
	4.2.4	<u>Residues in air</u>
	4.2.5	<u>Residues in body fluids and tissues of animal and human</u>

GLP	5.1	<u>Studies on absorption, distribution, excretion and elimination in mammals</u>
	5.2	<u>Acute toxicity</u>
GLP	5.2.1	<u>Oral</u>
GLP	5.2.2	<u>Percutaneous</u>
GLP	5.2.3	<u>Inhalation</u>
GLP	5.2.4	<u>Skin irritation</u>
GLP	5.2.5	<u>Eye irritation</u>
GLP	5.2.6	<u>Skin sensitization</u>
	5.3	<u>Short-term toxicity</u>
GLP	5.3.1	<u>Oral 28-day study</u>

GLP	5.3.2 <u>Oral 90-day study</u>
GLP	5.3.3 <u>Other routes</u>
	5.4 <u>Genotoxicity testing</u>
GLP	5.4.1 <u>In vitro studies</u>
GLP	5.4.2 <u>In vivo studies</u>
GLP	5.4.3 <u>In vivo studies in germ cells</u>
GLP	5.5 <u>Long term toxicity and carcinogenicity</u>
	5.6 <u>Reproductive toxicity</u>
GLP	5.6.1 <u>Multi-generation studies</u>
GLP	5.6.2 <u>Developmental toxicity studies</u>
GLP	5.7 <u>Delayed neurotoxicity studies</u>
	5.8 <u>Other toxicological studies</u>
GLP	5.8.1 <u>Toxicity studies of metabolites as referred to in the tion point</u>
GLP	5.8.2 <u>Supplementary studies on the active substance</u>
	5.9 <u>Medical data</u>
	5.9.1 <u>Medical surveillance on manufacturing plant personnel</u>
	5.9.2 <u>Direct observation, e.g. clinical cases and poisoning</u>
	5.9.3 <u>Observations on exposure of the general population and logical studies if appropriate</u>
	5.9.4 <u>Diagnosis of poisoning (determination of active e, metabolites), specific signs of poisoning, clinical tests</u>
	5.9.5 <u>Proposed treatment: first aid measures, antidotes, treatment</u>
	5.9.6 <u>Expected effects of poisoning</u>
	5.10 <u>Summary of mammalian toxicity and conclusion (including ved adverse effect level (NOAEL), acceptable daily intake cceptable operator exposure level (AOEL)) and maximum admissible ation in water. Overall evaluation with regard to all gical data, and other information concerning the active e</u>

GLP	6.1 <u>Metabolism, distribution and expression of residue in plants</u>
GLP	6.2 <u>Metabolism, distribution and expression of residue in livestock</u>
GLP*	6.3 <u>Residue trials</u>
GLP	6.4 <u>Livestock feeding studies</u>
	6.5 <u>Effects of industrial processing and/or household preparations</u>
GLP	6.5.1 <u>Effects on the nature of the residue</u>
GLP	6.5.2 <u>Effects on the residue levels</u>
GLP*	6.6 <u>Residues in succeeding crops</u>
	6.7 <u>Proposed maximum residue levels (MRLs) and justification of the acceptability of these residues.</u>
	6.8 <u>Proposed pre-harvest intervals for envisaged uses, or withholding periods or storage periods, in the case of post-harvest uses.</u>
	6.9 <u>Estimation of the potential and actual exposure through diet and other means</u>

	6.10	<u>Summary and evaluation of residue behaviour</u>
	7.1	<u>Fate and behaviour in the environment</u>
	7.1.1	<u>Route and rate of degradation</u>
GLP	7.1.1.1	<u>Route of Degradation</u>
GLP	7.1.1.1.1	<u>Aerobic degradation</u>
	7.1.1.1.2	<u>Supplementary studies</u>
GLP	7.1.1.2	<u>Rate of degradation</u>
GLP	7.1.1.2.1	<u>Laboratory studies.</u>
GLP	7.1.1.2.2	<u>Field studies</u>
	7.1.2	<u>Adsorption and desorption</u>
GLP	7.1.3	<u>Mobility in the soil</u>
GLP	7.1.3.1	<u>Column leaching studies</u>
GLP	7.1.3.2	<u>Aged residue column leaching</u>
	7.1.3.3	<u>Lysimeter Studies or Field leaching studies</u>
	7.2	<u>Fate and behaviour in water and air</u>
GLP	7.2.1	<u>Route and rate of degradation in aquatic systems (as far as far by point 2.9)</u>
GLP	7.2.1.1	<u>Hydrolytic degradation</u>
	7.2.1.2	<u>Photochemical degradation</u>
GLP	7.2.1.3	<u>Biological degradation</u>
GLP	7.2.1.3.1	<u>Ready biodegradability</u>
GLP	7.2.1.3.2	<u>Water/sediment study</u>
GLP	7.2.1.4	<u>Degradation in the saturated zone</u>
	7.2.2	<u>Rate and route of degradation in air (as far as not at 2.10)</u>
	7.3	<u>Definition of the residue</u>
	7.4	<u>Monitoring data</u>

	8.1	<u>Effects on birds</u>
GLP	8.1.1	<u>Acute oral toxicity</u>
GLP	8.1.2	<u>Short-term dietary toxicity</u>
GLP	8.1.3	<u>Subchronic toxicity and reproduction</u>
	8.2	<u>Effects on aquatic organisms</u>
GLP	8.2.1	<u>Acute toxicity to fish</u>
	8.2.2	<u>Chronic toxicity to fish</u>
GLP	8.2.2.1	<u>Chronic toxicity test on juvenile fish</u>
GLP	8.2.2.2	<u>Fish early life stage toxicity test</u>
GLP	8.2.2.3	<u>Fish life cycle test</u>
GLP	8.2.3	<u>Bioconcentration in fish</u>
GLP	8.2.4	<u>Acute toxicity to aquatic invertebrates</u>
GLP	8.2.5	<u>Chronic toxicity to aquatic invertebrates</u>
GLP	8.2.6	<u>Effects on algal growth</u>
GLP	8.2.7	<u>Effects on sediment dwelling organisms</u>
GLP	8.2.8	<u>Aquatic plants</u>
	8.3	<u>Effects on arthropods</u>
	8.3.1	<u>Bees</u>
GLP*	8.3.1.1	<u>Acute toxicity</u>
GLP*	8.3.1.2	<u>Bee brood feeding test</u>
GLP*	8.3.2	<u>Other arthropods</u>
	8.4	<u>Effects on earthworms</u>
GLP	8.4.1	<u>Acute toxicity</u>
GLP	8.4.2	<u>Sublethal Effects</u>
GLP	8.5	<u>Effects on soil non-target micro organisms</u>

GLP	8.6 <u>Effects on other non-target organisms (flora and fauna) believed to be at risk</u> 8.7 <u>Effects on biological methods for sewage treatment</u> ----- 9 <u>Summary and conclusions of points 7 and 8</u> ----- 10 <u>Proposals for labelling</u>
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ANNEX III

	<p>1.1 <u>Applicant (name and address, etc.)</u></p> <p>1.2 <u>Manufacturer of the preparation and the active substance(s) (names and addresses, etc. including location of plants)</u></p> <p>1.3 <u>Trade name or proposed trade name, and manufacturer's identification code number of the preparation if appropriate</u></p> <p>1.4 <u>Detailed quantitative and qualitative information on composition of the preparation (active substance(s), and formulants).</u></p> <p>1.5 <u>Physical state and nature of the preparation (e.g. concentrate, wettable powder, solution etc)</u></p> <p>1.6 <u>Function (herbicide, insecticide, etc.)</u></p> <p>-----</p> <p>2.1 <u>Appearance (colour and odour)</u></p> <p>2.2 <u>Explosivity and oxidizing properties</u></p> <p>2.2.1 Explosive properties of preparations</p> <p>2.2.2 Oxidizing properties of preparations</p> <p>2.3 <u>Flash point and other indications of flammability or spontaneous ignition</u></p> <p>2.4 <u>Acidity / alkalinity and if necessary pH value</u></p> <p>2.4.1 Acidity or alkalinity and the pH value</p> <p>2.4.2 pH of a 1% aqueous dilution, emulsion or dispersion of the preparation</p> <p>2.5 <u>Viscosity and surface tension</u></p> <p>2.5.1 Kinematic viscosity of ULV preparations</p> <p>2.5.2 Viscosity for non newtonian liquids</p> <p>2.5.3 Surface tension for liquid preparations</p> <p>2.6 <u>Relative density and bulk density</u></p> <p>2.6.1 Relative density of liquid preparations</p> <p>2.6.2 Bulk (tap) density of preparations which are powders or granules</p> <p>2.7 <u>Storage stability - stability and shelf-life: Effects of light, temperature and humidity on technical characteristics of the plant protection product</u></p> <p>2.7.1 <u>Stability of the preparation after storage (GLP for chemical stability only if on the basis of theoretical considerations hazardous products may be formed during storage)</u></p> <p>2.7.2 Additionally in the case of liquid products,</p> <p>2.7.3 the effect of low temperatures on stability The shelf life of the preparation at ambient</p>
GLP GLP	<p>2.8.1 <u>Wettability</u></p> <p>2.8.2 <u>Persistent foaming</u></p> <p>2.8.3 <u>Suspensibility and suspension stability</u></p> <p>2.8.4 <u>Dilution stability</u></p> <p>2.8.5 <u>Dry sieve test and wet sieve test</u></p> <p>2.8.6 <u>Particle size distribution (dustable and wettable granules), content of dust/fines (granules), attrition and abrasion</u></p> <p>2.8.6.1 Particle size distribution</p> <p>2.8.6.2 Dust content</p> <p>2.8.6.3 Friability and attrition</p> <p>2.8.7 <u>Emulsifiability, Re-emulsifiability, emulsion</u></p>

	<p>2.8.7.1 Emulsifiability, emulsion stability and re- lity</p> <p>2.8.7.2 Stability of dilute emulsions and of s which are emulsions</p> <p>2.8.8 <u>Flowability, pourability (rinsability) and</u></p> <p>2.8.8.1 Flowability of granular preparations</p> <p>2.8.8.2 Pourability (including rinsed residue)</p> <p>2.8.8.3 Dustability of dustable powders</p> <p>2.9 <u>Physical and chemical compatibility with other products including plant protection products with which its use is to be authorized</u></p> <p>2.9.1 Physical compatibility of tank mixes</p> <p>2.9.2 Chemical compatibility of tank mixes</p> <p>2.10 <u>Adherence and distribution to seeds</u></p> <p>2.11 <u>Summary and evaluation of data presented under points 2.1 to 2.10</u></p> <p>-----</p> <p>3.1 <u>Field of use</u></p> <p>3.2 <u>Effects on harmful organisms</u></p> <p>3.3 <u>Details of intended use</u></p> <p>3.4 <u>Application rate</u></p> <p>3.5 <u>Concentration of active substance in material used (e.g. in the diluted spray, baits or treated seed)</u></p> <p>3.6 <u>Method of application</u></p> <p>3.7 <u>Number and timing of applications and duration of protection</u></p> <p>3.8 <u>Necessary waiting periods or other precautions to avoid phytotoxic effects on succeeding crops</u></p> <p>3.9 <u>Proposed instructions for use</u></p> <p>-----</p> <p>4.1 <u>Packaging (type, materials, size etc.), compatibility of the preparation with proposed packaging materials.</u></p> <p>4.1.1 Packaging</p> <p>4.1.2 The suitability of the packaging, including closures</p> <p>4.1.3 The resistance of the packaging material to its contents</p>
GLP	<p>4.2 <u>Procedures for cleaning application equipment</u></p> <p>4.3 <u>Re-entry periods, necessary waiting periods or other protect man, livestock and the environment</u></p> <p>4.3.1 Where relevant pre-harvest intervals, re-entry periods periods</p> <p>4.3.2 Information on any specific agricul- health or environmental conditions under which the prepara-tion t be used must be provided.</p> <p>4.4 <u>Recommended methods and precautions andling, storage, transport or fire</u></p> <p>4.5 <u>Emergency measures in the case of an</u></p> <p>4.6 <u>Procedures for destruction or on of the plant protection product and its packaging</u></p> <p>4.6.1 <u>Possibility of neutralization</u></p> <p>4.6.2 <u>Controlled incineration</u></p> <p>4.6.3 <u>Others</u></p> <p>-----</p> <p><u>tical methods for the determination of pure active substances protection product</u> <u>and, where appropriate, for relevant breakdown</u></p>

		mers and impurities of the active substance and additives (e.g. and formulants
	5.2	<u>Analytical methods for the determination</u>

		cy data (see introduction point 3)

		e toxicity
	7.1.1	<u>Oral</u>
GLP	7.1.2	<u>Percutaneous</u>
GLP	7.1.3	<u>Inhalation</u>
GLP	7.1.4	<u>Skin irritation</u>
GLP	7.1.5	<u>Eye irritation</u>
GLP	7.1.6	<u>Skin sensitization</u>
GLP	7.1.7	<u>Supplementary studies for combinations</u>
GLP		ection products
	7.2	<u>Data on exposure</u>
	7.2.1	<u>Operator exposure</u>
	7.2.1.1	<u>Estimation of operator exposure</u>
	7.2.1.2	<u>Measurement of operator exposure</u>
GLP	7.2.2	<u>Bystander exposure</u>
GLP	7.2.3	<u>Worker Exposure</u>
	7.2.3.1	<u>Estimation of worker exposure</u>
	7.2.3.2	<u>Measurement of worker exposure</u>
GLP		
GLP	7.3	<u>Dermal absorption</u>
	7.4	<u>Available toxicological data relating to</u>
		stances

GLP*	8.1	<u>Residue trials</u>
GLP	8.2	<u>Livestock feeding studies</u>
GLP*	8.3	<u>Residues in succeeding crops</u>
	8.4	<u>Proposed maximum residue levels (MRLs) tion of the acceptability of these residues.</u>
	8.5	<u>Proposed pre-harvest intervals for s, or withholding periods or storage periods, in the case of uses.</u>
	8.6	<u>Estimation of the potential and actual through diet and other means</u>
	8.7	<u>Summary and evaluation of residue</u>

	9.1	<u>Fate and behaviour in the environment</u>
	9.1.1	<u>Rate of Degradation in Soil</u>
GLP	9.1.1.1	<u>Laboratory studies</u>
GLP	9.1.1.2	<u>Field studies</u>
	9.1.2	<u>Mobility in the Soil</u>
GLP	9.1.2.1	<u>Laboratory studies</u>
GLP	9.1.2.2	<u>Lysimeter Studies or Field leaching</u>
	9.1.3	<u>Estimation of expected concentrations in</u>
	9.2	<u>Fate and behaviour in water</u>
GLP	9.2.1	<u>Estimation of concentrations in</u>
	9.2.2	<u>Impact on water treatment procedures</u>

	9.2.3	<u>Estimation of concentrations in Surface</u>
GLP		
GLP	9.3	<u>Fate and behaviour in air</u>
GLP		-----
	10.1	<u>Effects on birds</u>
GLP	10.1.1	<u>Acute oral toxicity</u>
	10.1.2	<u>Supervised cage or field trials</u>
	10.1.3	<u>Acceptance of bait, granules, or treated</u>
GLP		s
	10.1.4	<u>Effects of secondary poisoning.</u>
GLP		
GLP	10.2	<u>Effects on aquatic organisms</u>
GLP	10.2.1	<u>Acute toxicity to fish, aquatic</u>
		<u>or effects on algal growth.</u>
GLP	10.2.2	<u>Microcosm or Mesocom study</u>
	10.2.3	<u>Residue data in fish</u>
	10.2.4	<u>Additional studies</u>
GLP*		
GLP*	10.3	<u>Effects on terrestrial vertebrates other</u>
GLP*		
GLP*		
GLP*	10.4	<u>Effects on bees</u>
	10.4.1	<u>Acute oral and contact toxicity</u>
	10.4.2	<u>Residue test</u>
GLP*	10.4.3	<u>Cage Tests</u>
	10.4.4	<u>Field tests</u>
GLP*	10.4.5	<u>Tunnel tests</u>
	10.5	<u>Effects on arthropods other than bees</u>
	10.5.1	<u>Laboratory, extended laboratory and</u>
		<u>sts</u>
	10.5.2	<u>Field tests</u>

	10.6	<u>Effects on earthworms and other soil</u>
		<u>cro-organisms, believed to be at risk.</u>
GLP	10.6.1	<u>Effects on earthworms</u>
GLP	10.6.1.1	<u>Acute toxicity tests</u>
GLP	10.6.1.2	<u>Tests for sublethal effects</u>
	10.6.1.3	<u>Field studies</u>
GLP	10.6.2	<u>Effects on other soil non-target</u>
		<u>macro-organisms</u>
GLP	10.7	<u>Effects on soil non-target micro-</u>
GLP		
	10.7.1	<u>Laboratory Testing</u>
	10.7.2	<u>Additional Testing</u>
	10.8	<u>Available data from biological primary</u>
		<u>screening in summary form</u>

	11.	SUMMARY AND EVALUATION OF SECTIONS 9 AND

	12.	Further Information