Fungicide Profile & Listing

Below is a survey of the major fungicide classes used in modern agriculture, their key active ingredients and uses, molecular targets and modes of action (MOA), known human-health hazards (with key biochemical, cellular, and metabolic interactions), typical toxicity levels, and a sketch of their main industrial syntheses.

1. Multi-site Contact Fungicides

Dithiocarbamates

- **Actives & Uses**: Mancozeb, maneb, zineb, Ziram—broad-spectrum protectants against early blight, scab, downy mildew on fruits, vegetables, ornamentals.

- **MOA**: Upon foliar deposition they form reactive metabolites (e.g. ethylenethiourea, ETU) that covalently modify multiple sulfhydryl-containing enzymes in fungal cells, collapsing metabolic pathways (Wikipedia).

- **Human Hazards**:
    - **ETU (metabolite)**: classified as a probable human carcinogen; induces oxidative DNA damage, thyroid disruption, teratogenicity in rodents; rat oral LD_{50} ≈ 62 mg/kg (PMC).
    - **Acute**: skin/eye irritation, mild neurotoxicity.
    - **Chronic**: goiter, developmental effects via endocrine-disruption at thyroid peroxidase.

- **Industrial Synthesis**: CS_2 + amine (e.g. ethylenediamine) → dithiocarbamate salt; complexed with Mn or Zn salts under alkaline conditions; isolated by crystallization (Wikipedia).

Phthalimides

- **Actives & Uses**: Captan, folpet—contact protectants for fruit scab, brown rot.

- **MOA**: Hydrolyze to phthalimide acid that reacts with thiol groups across multiple target enzymes.

- **Human Hazards**: low acute toxicity (LD_{50} ~ 2000 mg/kg) but phthalic byproducts implicated in endocrine disruption and allergic sensitization.

- **Synthesis**: Phthalic anhydride + thiocyanate/thiourea derivatives under heat → mixed imide thiocyanates; purified by recrystallization.

2. Methyl Benzimidazole Carbamates (MBCs)

- **Actives & Uses**: Carbendazim, thiophanate-methyl—systemic protection against ascomycetes (powdery mildew, apple scab, Fusarium spp.) (Wikipedia).

- **MOA**: Bind β-tubulin at residues Thr178 & Ser138, preventing α/β-tubulin polymerization and arresting mitosis in fungal hyphae (Nature).

- **Human Hazards**:
    - **Mammalian tubulin binding** (Kd ≈ 43 μM) → mitotic disruption in rapidly dividing cells; bone-marrow suppression, hepatotoxicity in high-dose animal studies (PMC).
    - **LD_{50} (rat, oral)** ≈ 640 mg/kg.

- **Industrial Synthesis**: Cyclization of o-phenylenediamine with methyl chloroformate (or equivalent cyanate) under acid catalysis → methyl benzimidazole-2-carbamate; purity > 99% via biphasic extraction (ScienceDirect).

3. Demethylation Inhibitors (DMIs / Triazoles)

- **Actives & Uses**: Tebuconazole, propiconazole, myclobutanil—broad-spectrum systemic fungicides for cereals, fruits, vegetables.

- **MOA**: Inhibit fungal cytochrome P450 14α-demethylase (CYP51), blocking ergosterol biosynthesis and destabilizing membranes (Wikipedia).

- **Human Hazards**:
    - **Endocrine disruption** via off-target human CYP inhibition (e.g. CYP19 aromatase), altering steroidogenesis; liver-enzyme induction, headaches, dizziness reported in applicators.
    - **LD_{50} (rat, oral)** typically > 1000 mg/kg.

- **Industrial Synthesis**: Nucleophilic displacement of chlorinated phenoxypropanol precursors by triazole moieties under basic conditions; refined by distillation and salt formation.

4. Quinone Outside Inhibitors (Qols / Strobilurins)

- **Actives & Uses**: Azoxystrobin, pyraclostrobin—systemic fungicides against foliar pathogens (rusts, mildews) in cereals, grapes, vegetables.

- **MOA**: Bind the Qo site of cytochrome bc_1 complex (complex III) in fungal mitochondria, halting electron transport and ATP synthesis (Wikipedia).

- **Human Hazards**:

    1. **Acute**: moderate oral toxicity (LD_{50} ≈ 5000 mg/kg), respiratory irritation.

    2. **Cellular**: at high concentrations can disrupt mammalian mitochondrial respiration, generating ROS and triggering apoptosis in vitro (Wikipedia).

- **Industrial Synthesis**:

    1. **Coupling** 2-chlorobenzonitrile + 4,6-dihydroxypyrimidine → pyrimidinyl ether intermediate.

    2. **Chlorination** → chloro-pyrimidine.

    3. **Ullmann-type etherification** with (E)-2-(2-hydroxyphenyl)-3-methoxyacrylate under Cu catalysis → azoxystrobin.

5. Succinate Dehydrogenase Inhibitors (SDHIs)

- **Actives & Uses**: Boscalid—broad-spectrum control of Botrytis, Alternaria, Septoria in fruits and cereals.

- **MOA**: Competitively bind the ubiquinone pocket of succinate dehydrogenase (complex II) in fungal mitochondria, blocking the TCA cycle and respiration (Wikipedia).

- **Human Hazards**:

    1. **Acute**: low toxicity (LD_{50} > 2000 mg/kg);

    2. **Chronic**: in vitro inhibition of mammalian SDH at high doses may cause mitochondrial dysfunction and neurotoxicity.

- **Industrial Synthesis**:

    1. **Suzuki coupling**: 1-chloro-2-nitrobenzene + 4-chlorophenylboronic acid → 2-nitrobiphenyl intermediate.

    2. **Reduction** → 2-aminobiphenyl.

    3. **Acylation** with 2-chloro nicotinoyl chloride → boscalid; optimized continuous-flow and one-pot processes improve yield and reduce solvent use.

6. Phenylamides (Phosphonyl Amines)

- **Actives & Uses**: Metalaxyl, mefenoxam—target oomycetes (Pythium, Phytophthora) in vegetables, ornamentals.

- **MOA**: Disrupt rRNA synthesis via unknown target (likely RNA polymerase I), blocking spore germination and mycelial growth (Wikipedia).

- **Human Hazards**:
    - **Moderate** acute toxicity (LD_{50} ~ 500–1000 mg/kg); hepatic metabolism via CYP2C9 produces oxo and hydroxy metabolites, potential oxidative stress.

7. Anilino Pyrimidines

- **Actives & Uses**: Cyprodinil, pyrimethanil—control of Botrytis, grey mold in grapes and berries.

- **MOA**: Inhibit methionine biosynthesis and secretion of fungal lytic enzymes; precise binding target remains under study (Wikipedia).

- **Human Hazards**: low acute toxicity (LD_{50} > 2000 mg/kg); possible skin sensitization; endocrine endpoints not well characterized.

8. Phosphonates / Fosetyl-Al

- **Actives & Uses**: Fosetyl-aluminium—“inducer” fungicide for downy mildew, Phytophthora spp.; acts both protectively and curatively.

- **MOA**: Hydrolyzed to phosphorous acid in planta → activates plant defense pathways (PR proteins), minimal direct antifungal activity (Wikipedia).

- **Human Hazards**: very low acute toxicity (LD_{50} > 2000 mg/kg); high doses can cause hyperphosphatemia, renal burden.

9. Copper & Sulfur

- **Actives & Uses**: Copper hydroxide, oxychloride; elemental sulfur—multi-site protectants for broad-leaf and fungal diseases.

- **MOA**: Copper ions disrupt protein function and membrane integrity; sulfur inhibits respiration and spore germination.

- **Human Hazards**: skin/eye irritant; chronic exposure may lead to cholestatic liver injury (copper) or respiratory irritation (sulfur dust).

- **Manufacture**: Copper salts from chalcopyrite roasting + acid leaching; sulfur mined or by-product of petroleum refining.

Comparative Toxicity & Persistence

Class	LD_{50} (rat, oral)	Persistence (soil $t_{1/2}$)	Bioaccumulation	Primary Human Target
Dithiocarbamates (ETU)	62 mg/kg	days–weeks	low–moderate	DNA, thyroid enzymes (ETU)
Phthalimides	~2000 mg/kg	days	low	Multiple thiol enzymes
MBCs	~640 mg/kg	weeks	low	Tubulin (mitosis)
Triazoles	> 1000 mg/kg	days–weeks	low	CYP51, human CYPs
QoIs	~5000 mg/kg	days–weeks	low	Mitochondrial bc_1 complex
SDHIs	> 2000 mg/kg	weeks	low	SDH (complex II)
Phenylamides	500–1000 mg/kg	weeks	low	Fungal RNA polymerase (indirect human)
Anilino Pyrimidines	> 2000 mg/kg	days–weeks	low	Fungal Met synth. (unclear human)
Fosetyl-Al	> 2000 mg/kg	days	negligible	Plant defense pathways
Copper / Sulfur	~300 mg/kg(Cu)	persistent (Cu)	moderate (Cu)	Protein thiols, cellular membranes

Why Manufacturing Matters

- **Hazardous Intermediates**: phosgene (triazoles), carbon disulfide (dithiocarbamates), methyl isocyanate (MBCs) require stringent containment.

- **Impurity Risks**: residual solvents (DMF, toluene), metal catalysts (Pd, Cu) can remain in technical grades, adding toxicity.

- **Scale-up Exposures**: large‑volume reactors amplify inhalation and dermal risks; accidental releases (e.g. ETU contamination) can impact workers and nearby communities.

Conclusion

Although fungicides exploit targets largely absent or divergent in mammals (ergosterol biosynthesis, fungal-specific tubulin, mitochondrial complexes), many share off-target interactions—most notably with human P450s, tubulin, and mitochondrial enzymes—that underlie their acute and chronic toxicities. Their industrial synthesis relies on highly reactive and often toxic intermediates, making rigorous process controls and post-synthetic purification critical to minimizing risks to applicators, workers, and consumers.