NAFOL 22+ Human Health Endpoints

Overview – NAFOL 22+ is a residual alcohol product is a by-product of the C20 alcohols manufacturing process. It is a UVCB substance that consists of several linear long chain alcohols, predominantly from C20 to C28. Eicosanol-1-ol (C20) ≤ 10%, docosanol-1-ol (C22) 45-65%, tetracosan-1-ol (C24) 19-31%, hexacosan-o-l (C26) 9-17%, and octacosan-1-ol (C28) ≤ 9% are the major components. These substances make up over 80% of the composition of NAFOL 22+. Other constituents include, to a much lesser extent, secondary long chain alcohols and complex mixtures of long chain carboxylate esters. Very few toxicology studies target the composition as a whole. However, the structural similarity and the known mammalian toxicity of specific of the individual long chain alcohols allows for evaluation of the toxicity of NAFOL 22+ that is both conservative and protective of human health.

From REACH registration efforts for the long chain alcohols a read-across evaluation for human health endpoints was established as the following:

MAMMALIAN TOXICITY			
Basic toxicokinetics	Eicosan-1-ol assessment	Docosan-1-ol assessment	Waiver
Acute Toxicity: Oral	LD50>10000 mg/kg	LD50> 2000mg/kg	No data Read-across
Acute Toxicity: Dermal	LD50> 10000 mg/kg	LD50> 10000 mg/kg	No data Read-across
Acute Toxicity: Inhalation	Not required	Not required	Waiver
Irritation: Eye/Skin	Not irritating	Not irritating	No data Read-across
Sensitisation	Not sensitising	Not sensitising	No data Read-across
Carcinogenicity	Not classified as a mutagen Category 3	Not classified as a mutagen Category 3	Waiver
Repeated dose toxicity: oral	NOAEL > 1000mg/kg	NOAEL > 1000mg/kg	No data Read-across
Genetic Toxicity	Negative	Negative	No data Read-across
Developmental Toxicity / Teratogenicity	NOAEL > 1000mg/kg	NOAEL > 1000mg/kg	No data Read-across

Acute oral toxicity – The acute oral toxicity of can be evaluated by review of the acute oral toxicity of ALFOL 20+ (CAS 1190630-03-05) which represents C18-26, predominantly C20 long chain alcohols. The non-guideline study (AKUTE TOXIZITAT VON ALFOL 20+ AN RATTEN BEI PERORALER VERABREICHUNG, 1975) established an LD_{50} > 12,500 mg/kg in rats for. The acute oral toxicity of NACOL 22 (CAS 661-19-8) which is docosanol-1-ol (C22 >98%)) is LD_{50} >10,000 mg/kg in the guideline OECD 401 GLP study (ACUTE TOXICITY-ORAL-OF NACOL 22 RD IN SPRAGUE-DAWLEY RATS, 1987). These two studies demonstrate that there is no acute oral toxicity concern for the lower molecular weight long chain alcohols or the major component alcohol in NAFOL 22+. The C16-18 and C22 long chain alcohols data fall are inharmony with the REACH read-across presented above.

Acute inhalation toxicity – Acute inhalation toxicity is not a concern for this product distribution because of the very low vapor pressure. Vapor pressure determinations for NAFOL 22+ established that the vapor pressure is <5 Pa @ 20 ^{o}C. (CHELAB Final Report, 2011). The very low vapor pressure is addressed in the REACH read-across with a waiver.

Acute dermal toxicity – Acute dermal toxicity studies are very rare because of animal rights concerns. One non-guideline study of ALFOL 16-18 (C16-24, predominantly C16 and C18) long chain alcohols (Toxicity Test Summary ALFOL 1618, Scientific Associates, 1968) established and LD50 >10,000 mg/kg in rats. The C16-18 long chain alcohols data fall are inharmony with the REACH read-across presented above.

Eye irritation -- Acute eye irritation was not noted in a study of the C22 long chain alcohol (EYE IRRITATION STUDY OF NACOL 22 RD IN THE RABBIT AFTER SINGLE INSTILLATION INTO THE CONJUCTIVAL SAC, 1986). The composition of NACOL 22 RD is the same as NACOL 22, >98% C22 long chain alcohol) In this study OECD 405 study very slight and transient erythema was noted with no lasting pathological findings. Likewise, the acute eye irritation was not noted in the study of the C20 long chain alcohol (EYE IRRITATION STUDY OF NACOL 20 IN THE RABBIT AFTER SINGLE INSTILLATION INTO THE CONJUCTIVAL SAC, 1986). In this study OECD 405 study very slight and transient erythema was noted with no lasting pathological findings. Finally, the C16-18 long chain alcohols (Toxicity Test Summary ALFOL 1618, Scientific Associates, 1968) did not observe eye irritation. The C16-18, C20, and C22 long chain alcohols data fall are inharmony with the REACH read-across presented above.

Skin irritation – Skin irritation was not noted for the C20 long chain alcohol (ACUTE SKIN IRRITATION/CORROSION TEST (PATCH-TEST) OF NACOL 20 IN THE RABBIT, 1986), with NACOL 20 having >95% C20 long chain alcohols. The C16-18 long chain alcohols (Toxicity Test Summary ALFOL 1618, Scientific Associates, 1968) did not observe skin irritation. The C16-18 and C20 long chain alcohols data fall are inharmony with the REACH read-across presented above.

Skin sensitization – The results of a Magnusson and Kligman test for delayed dermal sensitization indicate that C20 and C22 long chain alcohols does not elicit a sensitization response in the guinea pig. (NAFOL 2022 DELAYED DERMAL SENSITIZATION IN THE GUINEA PIG (MAGNUSSON AND KLIGMAN TEST), 2000). NAFOL 2022 The C18 - C22 long chain alcohols data fall are in harmony with the REACH read-across presented above.

Developmental toxicity – there is scarce extant study data for the developmental toxicity of long chain alcohols. This is to be expected because of lack of biological activity for these molecules. There is an expert statement for 1-tetracosanol and 1-hexacosanol that reflects "All available data from the published peer-reviewed literature indicate that long chain fatty alcohols in general are of insignificant toxicity. There are extensive toxicology data on I-Docosanol indicating that this product is practically non-toxic. There are also limited safety/toxicity data on 1- hexacosanol and policosanols (which contain all 3 fatty alcohols) that also indicate no discernible toxicity of these products either in vitro or in vivo in animals or humans, The chemical structure of I-Docosanol (C22:0) is similar to the longer chain length fatty alcohols: 1- Tetracosanol (C24:0) and 1-Hexacosanol (C26:0), and therefore is expected to exhibit similar physical/chemical properties and toxicological behaviour to these members of the common group of policosanol alcohols" (EXPERT STATEMENT -SURROGATE TOXICOLOGICAL DATA 1-TETRACOSANOL (CASRN 506-51-4) and HEXCOSANOL (CASRN 506 52-4), 2004).

Repeated dose toxicity – A high quality 90-day repeated dose toxicity study was completed in 2021 for ALFOL 20+. This GLP OECD 408 study "90-DAY REPEATED DOSE ORAL TOXICITY STUDY IN WISTAR RATS with ethene, homopolymer, oxidized, hydrolyzed, distn. residues, from C16-18 alcs. Manufacture" demonstrated that "On the basis of this 90-day repeated dose oral toxicity study with Ethene, homopolymer, oxidized, hydrolyzed, distn. residues, from C16-18 alcs. manuf. in male and female Wistar rats with dose levels of 100, 300, and 1000 mg/kg body weight day the following conclusions can be made: No test item-related mortality was observed and no toxicological effects of the test item were found for male and female clinical observations, functional observations, body weight development, food consumption, hormone analysis, haematology and coagulation, clinical biochemistry, urinalysis, gross macroscopic findings at necropsy and organ weights in all treated dose groups. At the histopathology evaluation no test item-related changes were observed. The no observed adverse effect level (NOAEL) of the test item in this study is considered to be 1000 mg/kg body weight/day. Report, BSL Munich Study No. STUGC20AA0542. These results are in harmony with the REACH read-across presented above.