ASCEND®

PERFORMANCE MATERIALS

# FlexaTrac™NTA

# Product Stewardship Summary

**August 2, 2019**

**Version 6**

Ascend Performance Materials is a United States based chemical company with global focus. We are focused more than ever before on our customers – to understanding their unique challenges in the market, to developing product solutions that address their market needs, and to providing excellent customer and technical service. For more information on our products please visit **www.ascendmaterials.com**.

Ascend Performance Materials
1010 Travis Street, Suite 900
Houston, TX 77002
1-713-315-5700

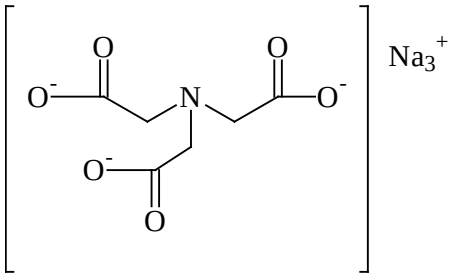
Product Stewardship
1-850-968-8411
**stewardship@ascendmaterials.com**

RESPONSIBLE CARE®
OUR COMMITMENT TO SUSTAINABILITY

Ascend Performance Materials is a member company of the American Chemistry Council. Ascend is committed to the principles of Responsible Care® and to the proper stewardship of its products. This document is intended to provide the user with access to health and safety information on Ascend's products. ACC is not responsible for the content of this document and does not warrant the accuracy of information posted in this or other similar documents. Information for the chemical(s) listed has been developed independently by each company (or in some cases, a group of companies). Each company is responsible for the content of its own product stewardship summary. For more information about the content of this document, users should contact Ascend Performance Materials.

# *FlexaTrac-NTA Product Stewardship Summary*

| | |
|---|---|
| *Chemical Family*: | Aminocarboxylate |
| *Chemical Name*: | Glycine, N,N-bis(carboxymethyl)-, trisodium salt, monohydrate |
| *Synonyms*: | Sodium nitrilotriacetate; NTA-$Na_3$ |
| *CAS. No*: | 18662-53-8 (Anhydrous)<br>5064-31-3 (Monohydrate) |
| *Formula*: | $N(CH_2COO^-Na^+)_3 \bullet H_2O$ |



## *Introduction*

FlexaTrac-NTA is a trisodium salt of nitrilotriacetic acid and has been used as a chelating (binding) agent for more than 50 years. Nitrilotriacetate is used worldwide in a variety of market areas, with major emphasis in the detergent industry. FlexaTrac-NTA effectively controls a variety of metal ions in wash water thus allowing cleaning ingredients to work better. FlexaTrac-NTA also works well in the following applications:

- Laundry detergents
- Automatic dishwashing products
- Scale control in boiler water treatment
- Bottlewash formulations for removal of trace contaminating metal salts
- Carpet cleaning products
- Hard surface cleaners
- Metal cleaning and treatment
- Petroleum production and refining processes
- Thermochemical pulp processes
- Removal of hydrogen sulfide from natural gas (gas scrubbing)
- Polymer processing
- Textile scouring, bleaching and dyeing processes
- Vehicle washing products
- Natural gas fracking formulations (corrosion control)

## *Health Effects Overview*

FlexaTrac-NTA is one of the most extensively studied chemicals in the world. Hundreds of studies have been conducted by government agencies, academic institutions and industry. These studies have shown:

- FlexaTrac-NTA is safe for worker and consumer exposure when used responsibly
- FlexaTrac-NTA does not pose an occupational or consumer risk for cancer
- FlexaTrac-NTA's, in high dose, long term animal studies, has been related to urinary tract tumors. These effects have been shown to be due to metal toxicity.

- FlexaTrac-NTA does not pose occupational risks when properly controlled through engineering and administrative controls and personal protective equipment
- FlexaTrac-NTA's waste treatment decomposition products do not pose a secondary danger to human health.

## *Environmental Effects Overview*

Through many studies conducted around the world, FlexaTrac-NTA has been shown to have no negative effects on the environment when manufactured, formulated and used in a responsible manner. The studies have determined:

- FlexaTrac-NTA is not persistent in the environment, and poses no risks to the environment from consumer and industrial use
- FlexaTrac-NTA is readily broken down in both aerobic and septic waste disposal systems
- FlexaTrac-NTA is readily biodegradable in freshwater and saltwater aquatic environments
- FlexaTrac-NTA is readily biodegradable in anaerobic conditions
- FlexaTrac-NTA undergoes photo and chemical degradation.
- FlexaTrac-NTA ultimately breaks down into carbon dioxide, water and inorganic nitrogen
- While the above facts are true for FlexaTrac-NTA as sold, they are also true for metal complexes of FlexaTrac-NTA
- Due to its rapid biodegradation FlexaTrac-NTA has been shown to have little effect on the mobilization of heavy metals in the sewage treatment or aquatic environments
- While studies show that FlexaTrac-NTA is toxic to algae, these effects are related to mineral starvation. These effects would never be seen in the natural environment due to gross excess of metals in the aquatic environment.

## *Physical Properties Overview*

FlexaTrac-NTA is available as a free flowing powder or 40% water solution. These products obviously have different properties and handling characteristics. Both products are classified as not regulated for transport, and can be shipped by any method. FlexaTrac-NTA's properties have been well characterized:

- FlexaTrac-NTA powder is a monohydrate under most circumstances
- FlexaTrac-NTA powder is not flammable or combustible. FlexaTrac-NTA powder is not a dust explosion risk.
- FlexaTrac-NTA, if heated to decomposition, breaks down into carbon, carbon dioxide, nitrogen oxides, and water.
- FlexaTrac-NTA powder contains a distribution of particle sizes
- FlexaTrac-NTA powder is highly water soluble (457 grams FlexaTrac-NTA per liter of solution at 20°C)
- FlexaTrac-NTA powder, if spilled, can be slippery if it becomes damp.
- FlexaTrac-NTA solution is a low viscosity fluid
- FlexaTrac-NTA solution is non-flammable and not corrosive to metals in normal use and storage conditions.

## *Worker Protection Overview*

FlexaTrac-NTA, in powder or liquid form, should be handled with proper industrial care in the formulation stages. Once mixed in a formulation, it is likely that other ingredients pose higher hazards than FlexaTrac-NTA. The following common sense measures should be used when handling FlexaTrac-NTA:

- **Engineering Controls** – Equipment should be designed to contain FlexaTrac-NTA. For FlexaTrac-NTA powder proper ventilation, dust control, collection and disposal is important. For FlexaTrac-NTA solution, spill control is essential.
- **Administrative Controls** – Proper equipment and chemical handling training is essential for minimizing exposure to any chemical, including FlexaTrac-NTA
- **Personal Protective Equipment** – Worker protections such as dust masks, gloves and other clothing, along with eye/face protection form the last line of defense against exposures.

## ***Ascend invites you to review the data presented. Please contact us if you have any additional questions.***


# *FlexaTrac-NTA*

## Human Health Profile

## *Conclusion of Safety for Use*

FlexaTrac-NTA is one of the most extensively studied chemicals in the world. Based on these many studies, multiple government agencies and academic organizations have concluded that the use of FlexaTrac-NTA is safe:

- In 1979, the United States Environmental Protection Agency conducted a risk assessment of FlexaTrac-NTA in consumer laundry formulations, and desired that no regulatory action was needed.
- In 1985, a review and analysis of FlexaTrac-NTA data by Universities Associated with Research and Education in Pathology (UAREP) concluded that use of FlexaTrac-NTA in consumer laundry formulation posed no practical risk to the public.
- In 1991 the World Health Organization established a drinking water guideline for FlexaTrac-NTA of 150μg/L which is well above the concentrations of FlexaTrac-NTA currently found in the environment (<10μg/L)[1].
- California OEHHA recognized in 1994 that there is a safe use level for FlexaTrac-NTA. The agency responsible for Prop 65 has set a "No Significant Risk Level" (NSRL) level of 70 μg/day[2,3]. Uses of FlexaTrac-NTA which result in bodily uptake of less than 70 μg/day do not require a Prop 65 warning label.
- In 1994, the Agricultural University Wageningen (The Netherlands) commissioned a study of the use of FlexaTrac-NTA in detergents. The university study concluded that no adverse effects on human safety are to be expected, and that the use of FlexaTrac-NTA as a builder in washing and dishwashing detergents leads to exposures which are more than 100000 times below toxicity risk levels. They also concluded that there was no appreciable risk to workers during the manufacture and formulation of FlexaTrac-NTA and products which contain it[4].
- Germany's 2008 Risk Assessment of FlexaTrac-NTA concludes that while certain occupational risks need adequate control, there is no need for further work for reducing risks to consumers[5].
- Under the 31st adaptation to the Dangerous Substances Directive, the European Commission established a labeling thresholds of 5% or more for any warning concerning FlexaTrac-NTA's suspect carcinogenicity, 20% or more for any warning concerning eye irritation, and 25% or more for any "Harmful if Swallowed" labeling[6].
- In the EU's Classification and Labeling regulation (2010), this 5% suspect carcinogen labeling threshold has been retained[7]. This confirms the recognition that there is a threshold to any health concerns with FlexaTrac-NTA.
- In 2010, Environment Canada and Health Canada conducted a review of the acid form of FlexaTrac-NTA, relying on FlexaTrac-NTA salt data. Environment Canada concluded that commercial use of the acid form of FlexaTrac-NTA did not pose a risk to human or environmental health[8].

## *Details on Health Effects*

Many of the studies conducted in FlexaTrac-NTA address concerns about long term health and environmental effects related to consumer exposure and waste water treatment and disposal. While some of these studies have shown health effects in animals, after long term, high dose exposure, these effects have never been seen in man, and are well understood.

## Animal Studies – Cancer

Investigation of carcinogenic effects of both the salt and acid versions of FlexaTrac-NTA began in the early 1970's. Seven cancer studies have been conducted on FlexaTrac-NTA, in both rats and mice. While FlexaTrac-NTA has been shown to cause cancer in some of these studies, these results were always at the highest exposure levels, after chronic exposure.

**Proctor and Gamble** – P&G scientists first investigated FlexaTrac-NTA's cancer effects in 1970; these results were published in 1972[9]. This study exposed male and female rats for 2 years to a diet containing up to 0.5% FlexaTrac-NTA. This study concluded that renal effects were the primary effect seen, but found no statistically significant level of cancer.

**National Cancer Institute** – The U.S. National Cancer Institute (NCI) ran several studies of FlexaTrac-NTA in the mid 1970's[10]. In these studies, both male and female rats and mice were fed doses of FlexaTrac-NTA for 18 or 24 months. Both the trisodium salt and the acid forms were tested. After prolonged ingestion of the highest doses of FlexaTrac-NTA (2% or 1.5% in the diet for 24 or 18 months), some of the rats and mice developed tumors of the kidney and urinary tract. The tumors were only significant in the highest dose levels tested – 2% FlexaTrac-NTA in the diet for rats, and 1.5% FlexaTrac-NTA in the diet for mice. As a result of these studies, FlexaTrac-NTA was placed on the U.S. National Toxicology Program (NTP) list of carcinogens.

Following the designation of FlexaTrac-NTA as a carcinogen by the National Toxicology Program, in 1980 the United States Environmental Protection Agency, conducted an in-depth review of FlexaTrac-NTA. The result of this review was that EPA viewed the cancer risk from FlexaTrac-NTA to be negligible, and would not pursue further regulatory action[11,12]. In 1980 the EPA risk assessment was discussed in hearings before the United States Congress. In written testimony for this EPA review, Dr. John Weisburger, one of the designers of the NCI cancer study, summarized the results of the NCI study. His stated position was that "…it is quite certain that the use of this material [FlexaTrac-NTA] as an ingredient in detergents does not constitute any risk whatsoever" and that EPA made the correct decision to allow the use of FlexaTrac-NTA because "…use of FlexaTrac-NTA in the detergent industry did not constitute a general human cancer risk..."[11]. The basis of this was:

- The dose level required to induce cancer was extremely high, at the maximum tolerated dose;
- In real world exposure, the crystalline material which formed in the urinary system of the rats could not form, due to its solubility and expected use levels of FlexaTrac-NTA; and
- The rapid biodegradation of the material would eliminate concerns from secondary environmental exposure.

**NCI Goyer Drinking Water Study** – In 1981 a study of FlexaTrac-NTA exposure in drinking water was published[13]. In this study, a large group of rats was fed drinking water containing 1000 ppm FlexaTrac-NTA. Exposure occurred for two years. Statistically significant cancers occurred in the kidneys of the rats. Although the FlexaTrac-NTA level in the drinking water was lower than the FlexaTrac-NTA level in food in the NCI and P&G feeding studies, cancers occurred. A likely cause is a common, natural kidney progression in male rats (advancing chronic nephrosis), which causes an increase in water consumption[14]. Thus, over the course of the study, the rats drank more and more water, increasing their dose.

**IARC** – In 1990, the International Agency for Research on Cancer (IARC) determined that FlexaTrac-NTA was a category 2B Carcinogen[15]. IARC 2B is a broad category, which contains substances which IARC scientists have determined are possibly carcinogenic to humans. It includes substances, such as FlexaTrac-NTA, for which there is sufficient evidence of cancer effects in animal studies, with inadequate evidence in humans. It also includes some substances which show limited evidence of cancer effects in humans. Other substances or conditions with this same designation are gasoline, diesel fuel, coffee and exposure of radiation from cellular phones. It is interesting that coffee's effects were also on the urinary tract, and are based on human, not animal data. There are many substances or circumstances which people are exposed to daily, which have more severe IARC ratings – Alcohol drinking, Estrogen therapy, Estrogen/Progesterone contraceptives and hormone therapy and Tobacco smoke (IARC 1 – Known to cause cancer in humans); Working as a hairdresser or barber, ingestion of Nitrate/Nitrite meat preservatives, and Shift Work (IARC 2A – Probably carcinogenic to humans)[16].

IARC reviewed FlexaTrac-NTA again in 1999. Although the IARC scientists present at the meeting have stated that the consensus was that FlexaTrac-NTA met the criteria for being downgraded to an IARC 3 (Not classifiable as to its carcinogenicity to humans), no vote on FlexaTrac-NTA was taken[17]; however IARC scientists did agree that toxic effects of Copper and Iron complexes of FlexaTrac-NTA were due to the metal, not the chelant. While FlexaTrac-NTA remained an IARC 2B carcinogen, data for effects related to copper and iron toxicity were removed from thee monograph[18].

**United Nations** – In 1991, the United Nations conducted a study to investigate substitutes for phosphate in detergent products. FlexaTrac-NTA was one of only a few compounds that met the stringent criteria set forth by the United Nations and considered a possible phosphate substitute in product formulations[19]. The United Nations report reviewed FlexaTrac-NTA consumer and worker exposure, combined with all available cancer data, and concluded that FlexaTrac-NTA use was safe based on anticipated use and exposure patterns.

## Human Data and Experience

FlexaTrac-NTA has been used in a wide variety of industrial, institutional and consumer products since the early 1970's. While animal data has shown this cancer risk at high levels of chronic exposure, no cancer evidence has been seen in humans. This fact has been recognized in several government risk assessments. Epidemiology studies of workers in a FlexaTrac-NTA production unit in the United States show no increased incidence of cancer among workers[20].

# *Why Is FlexaTrac-NTA Related to Cancer in Animals, at High Doses?*

The mechanism of tumor formation (sometimes called the Mode of Action, or MOA) varies by location within the urinary tract. As a chelating agent, FlexaTrac-NTA has the ability to bind with certain metals, including calcium, zinc and iron. It has been shown that it is the interaction of certain metals (calcium and zinc) and the cells of the urinary system that causes tumor formation after long term, high dose exposure in animals. FlexaTrac-NTA, like many chelants, plays a role in the transport of these metals. Extensive discussion of tumor mechanism can be found in a 1985 review article[14], and is summarized here.

**Kidney Tumors** – Within the rat body, in these high dose studies, FlexaTrac-NTA binds with zinc in many parts of the body, and this complex travels through the blood stream. Within the kidney, the FlexaTrac-NTA-Zinc complex goes through a cycle of filtration and re-absorption, in which the FlexaTrac-NTA is eliminated through the urine and most of the Zinc is deposited in the renal tubular cells. These cells essentially experience zinc poisoning; they die, and the result of this injury is a proliferation of other cells. This uncontrolled cell growth is a tumor. Effects which are almost identical occur when rats are exposed to high dietary zinc without FlexaTrac-NTA.[21] It has been clearly demonstrated that there is a clear threshold to these effects, and that they are only seen in high dose, long term studies.

**Urethral and Bladder Tumors** – Similar to the situation which exists with the renal tubular cells of the kidney, in the later parts of the urinary system of the rat, FlexaTrac-NTA binds with metal, creating an environment which leads to cell injury, death and tumor response. In the cells lining the urethral and bladder system, in the high dose animal studies, FlexaTrac-NTA complexes with and removes calcium. This loss of calcium causes certain cell functions to no longer work properly, causing rapid cell proliferation.[21] Studies have shown that these tumors can only occur at even higher levels of FlexaTrac-NTA exposure than the Kidney tumors.

# *What Does This Data Mean?*

## Risk Versus Hazard

While FlexaTrac-NTA has been shown to have these effects in long term animal studies, what is the risk that such effects would be seen in workers or consumers? A chemical hazard is the potential to cause harm, regardless of likelihood. Chemical risk is the likelihood that such an effect could happen in real life circumstances. The process of determining what the risk of a chemical is, and how to control that risk is called a risk assessment, and is a critical part of decision making for the use of any chemical. Performing a proper risk assessment is especially important when assessing human risk for a chemical which has only shown effects after extreme exposures in animals, such as FlexaTrac-NTA.

Although FlexaTrac-NTA is designated as an animal carcinogen, this designation must be taken in context of the true risk of FlexaTrac-NTA to human health. In rats and mice, cancer effects have only been seen in very high doses, for exposure of 1-1/2 to 2 years. Even when scaled to represent appropriate numbers for human health risk assessment, these doses would never be seen in real life conditions. Such critical review has led to the conclusions mentioned above – that multiple, worldwide government agencies and universities have determined that consumer and occupational exposure to FlexaTrac-NTA is safe.

Also to be considered is that other chelants have not been tested for cancer effects or have not been tested at the high levels of exposure used in the NCI study[22]. EDTA was not evaluated by NCI at doses similar to FlexaTrac-NTA because of its toxicity; EDTA would have caused acute toxicity, confounding any cancer findings[11]. FlexaTrac-NTA's cancer testing level was determined by finding the Maximum Tolerated Dose (MTD) – this is the dose which does not kill the animals outright, or cause significant health effects[10]. NCI scientists wrote that "…Since Na3FlexaTrac-NTA.H2O was thus determined to be relatively nontoxic…" such a high dose was tested. FlexaTrac-NTA's MTD dose is very high, while EDTA's MTD Dose is lower. EDTA showed non-lethal, toxic intestinal effects at a level of 0.75% in rat feed, while FlexaTrac-NTA showed similar effects at 1.5% in rat feed[22].

## *Government Risk Assessments*

Officials and agencies from various governments around the world have stated that FlexaTrac-NTA's use in detergents (including consumer applications) pose little or no risk to public health. In risk assessments conducted by governments in the United States, Canada, Germany (for the European Union) and California, as well as the World Health Organization FlexaTrac-NTA has been reviewed critically, and has been determined to be of acceptable risk in formulated products. Safe use and dosage levels have been set in the European Union and California, and industry standards in Canada.

### United Nations

In 1991, the World Health Organization performed a risk assessment to determine an acceptable level of FlexaTrac-NTA in drinking water. In their review of the cancer data, they state that the mechanisms summarized above are valid, and WHO decided that they would not use cancer as the basis for their guideline value for drinking water concentration. They decided that the basis would be non-cancerous kidney effects, but they did add a larger uncertainty factor to the assessment. WHO states that the factor is "probably conservative" which means that it overestimates the risk of FlexaTrac-NTA in drinking water. The WHO set a drinking water Total Daily Intake level of 10 µg/kg of body weight, and determined that a daily drinking water dose level of 150 µg/l was safe.[1]

### United States

In 1979, the United States Environmental Protection Agency conducted a risk assessment of FlexaTrac-NTA used in consumer laundry detergents. This assessment addressed health concerns for both workers (preparation of detergents) and consumers (using FlexaTrac-NTA containing detergents in the home). This risk assessment concluded that FlexaTrac-NTA's actual exposure to workers and consumers was below levels of concern. After the risk assessment was concluded, the Assistant Administrator for the EPA office responsible wrote that "…EPA sees no reason to take regulatory action against the resumed production and use of this substance for laundry detergents."[11]

The United States Food and Drug Administration (FDA) has reviewed the safety of FlexaTrac-NTA as a scale control additive in boilers which supply food contact steam to food production facilities. FlexaTrac-NTA may be used at a maximum of 5 ppm in the boiler feedwater, and cannot be used in systems which supply steam to dairy production facilities[23].

### California

In 1989, California added FlexaTrac-NTA to the Prop 65 list, due to its status as a possible carcinogen under IARC. In 1994, California's Office of Environmental Health Hazard Assessment determined that based on all available cancer data, FlexaTrac-NTA has a threshold below which they have no regulatory or public health concern. This level, the No Significant Risk Level or Safe Harbor Level, was set at 70 µg/day bodily uptake. This level is not the use level in a product; it is the level which is taken into the body by any route – dermal, ingestion or inhalation, which is not expected to result in an increased risk of cancer over a 70 year lifetime of daily uptake.

It is important to note that exposure which is modeled or measured to be below this level does not require Prop 65 warnings. While each customer or formulator should determine if formulated products containing FlexaTrac-NTA will result in exposures above this level, in 1996 Monsanto commissioned a

modeling study of typical FlexaTrac-NTA uses, and found that no uses resulted in exposure which exceeded this threshold. This data is discussed below in the Non-Government Risk Assessment section.

## New York

In the mid 1980's, the State of New York's Department of Environmental Conservation made the decision to ban FlexaTrac-NTA (Acid form) from household cleansing products offered for sale in the Sate of New York[24]. While there were many reasons, scientific and political, for this decision, it was based on the fear that widespread use of FlexaTrac-NTA in household formulations could lead to contamination of groundwater, primarily on Long Island. This fear, combined with the then relatively new cancer study results, led to much public debate and the eventual ban. While the ban is intended for household cleaning products, the broad definition of "Household Cleansing Products" has been a barrier for FlexaTrac-NTA products in New York.

Regulation Chapter X, Part 659.1 – Definitions
Household cleansing product shall mean any product, including but not limited to, soaps and detergents containing a surfactant as a wetting or dirt emulsifying agent and used primarily for domestic or commercial cleaning purposes, including but not limited to the cleansing of fabrics, dishes, food utensils and household and commercial premises.

Regulation Chapter X, Part 659.3 – Prohibitions
No household cleansing product containing nitrilotriacetic acid (FlexaTrac-NTA) in excess of a trace quantity shall be distributed, sold, offered or exposed for sale in this State.

Please see the Environmental Effects portion of this document for a discussion of FlexaTrac-NTA's inherent biodegradation properties. Much of the available groundwater degradation data was generated after the New York decision, and shows that under typical circumstances FlexaTrac-NTA is completely degraded in groundwater environments.

## Australia

FlexaTrac-NTA is allowed for unrestricted use in formulations and industrial applications in Australia. No formal risk assessment has been conducted.

## Canada

FlexaTrac-NTA is allowed for unrestricted use in I&I and consumer cleaning formulations in Canada. In the 1970's and 1980's FlexaTrac-NTA was reviewed several times by the Canadian government, for human health and environmental parameters[25,26]. Under Health Canada's WHMIS Classification System, Ascend classifies FlexaTrac-NTA as D2A Very Toxic – Due to the carcinogen classification, and also D2B Toxic – Due to irritation of the eyes from FlexaTrac-NTA dust.

Canada's Ecologo™ program has recognized that FlexaTrac-NTA's inclusion in Industrial & Institutional and Consumer Laundry formulations[27] and Commercial Car Wash formulations[28] is acceptable.

## China

FlexaTrac-NTA is allowed for unrestricted use in formulations and industrial applications in China. No formal risk assessment has been conducted.

## Germany and the European Union

The European Union Risk Assessment, performed by the German national risk assessment body (BAuA) concluded twice that below a use level of 5%, no suspect cancer labelling is required[5], because there is no practical cancer risk to human health. Use is permitted above 5%, but requires the suspect carcinogen labelling (R40 phrase under the Dangerous Substances Directive, H351 phrase under the CLP Regulation). Use in consumer formulations was also allowed.

## Japan

FlexaTrac-NTA is allowed for unrestricted use in formulations and industrial applications in Japan. No formal risk assessment has been conducted.

## Korea

Korea has reviewed FlexaTrac-NTA, and considers it to be an Observational Chemical. Korea allows its use for cleaning and industrial uses; however since it is on the Observational List, importers must register and maintain certain records with the Korean Ministry of the Environment.

## Switzerland

The Swiss Health Authority has reviewed FlexaTrac-NTA, and found it to be a class 4 substance[29]. Swiss regulations allow the use of FlexaTrac-NTA in cleaning and industrial formulations. A formulator is required to label products which contain FlexaTrac-NTA in practical amounts (greater than 0.1% in general cleaning products, greater than 0.2% in laundry products)[30]

## Taiwan

FlexaTrac-NTA was added to the newly created Chemical Inventory in Taiwan, and may be used in cleaning formulations and industrial applications without restriction. No formal risk assessment has been conducted.

# *Non-Government Risk Assessment*

The governmental conclusions that FlexaTrac-NTA is safe as used in the detergent industry are supported by industry risk assessment. These assessments, performed in a variety of ways (data review and modeling of typical use patterns) have shown FlexaTrac-NTA to be of little to no risk for occupational and customer uses.

## Universities Associated for Research and Education in Pathology

In 1985, a review and analysis of available FlexaTrac-NTA data was conducted by Universities Associated with Research and Education in Pathology (UAREP), an independent scientific organization made up of scientists from 15 universities across the United States. UAREP performed an extensive review of FlexaTrac-NTA's human health and safety and concluded that at concentrations present in the environment FlexaTrac-NTA "does not pose a practical risk to human health". Their report stated that the threshold of carcinogenic effects in rats "…is more than one million times higher than anticipated levels of human exposure" and that the cancer risk for man would be of no practical significance. [31]

## Agricultural University Wageningen

In 1994, industry asked the Agricultural University Wageningen (The Netherlands) to conduct an ecological and toxicological review of available FlexaTrac-NTA data. This review concluded that, from the production of FlexaTrac-NTA, no adverse human health effects are expected. Further conclusions were that use of FlexaTrac-NTA in consumer laundry and dishwashing formulations would result in exposures which were 100,000 times below toxicity risk levels. [32]

## Monsanto Exposure Modeling

In 1996, the Monsanto Company asked the risk assessment group of Cantox (now part of Intertek) to perform robust modeling of typical uses of FlexaTrac-NTA. This study was to determine if commercial use of FlexaTrac-NTA resulted in exposure which would require a Prop 65 warning label. The results showed that for all uses studied, no warning label was required. The result which was closest to 70 µg/day was 42.4 µg/day, for hard surface and floor cleaners which contain 25% FlexaTrac-NTA in the formulation[33].

| | | Deterministic Results | Stochastic Results | | |
|---|---|---|---|---|---|
| Use Conditions | NTA Formulations (%, weight/weight) | Point Estimate (µg/day uptake) | Mean (µg/day uptake) | Standard Deviation | 50th Percentile (Median) |
| Dishwashers/Bottle Rinsers - Powder | 25 | 7 | 6.6 | 3.57 | 6.1 |
| Dishwashers/Bottle Rinsers - Liquid | 25 | 2.18 | 1.93 | 2.15 | 1.21 |
| Laundromat Workers - Powder | 25 | 7.05 | 6.66 | 3.54 | 6.1 |
| Laundromat Workers - Liquid | 25 | 3.26 | 2.21 | 2.31 | 1.45 |
| Carpet Cleaners - Powder | 25 | 9.3 | 8.9 | 4.27 | 8.35 |
| Carpet Cleaners - Liquid | 25 | 21.2 | 18.9 | 15.1 | 14.8 |
| Floor Cleaners - Powder | 25 | 9.3 | 8.9 | 4.27 | 8.35 |
| Floor Cleaners - Liquid | 25 | 42.4 | 37.4 | 30.7 | 28.7 |
| Upholstery Cleaners - Powder | 25 | 9.3 | 8.9 | 4.27 | 8.35 |
| Upholstery Cleaners - Liquid | 25 | 21.2 | 18.9 | 15.1 | 14.8 |
| Hard Surface Cleaners - Powder | 25 | 9.3 | 8.9 | 4.27 | 8.35 |
| Hard Surface Cleaners - Liquid | 25 | 42.4 | 37.4 | 30.7 | 28.7 |
| Vehicle Cleaners - Powder | 25 | 7 | 6.6 | 3.57 | 6.1 |
| Vehicle Cleaners - Liquid | 25 | 2.18 | 1.93 | 2.15 | 1.21 |
| Manufacture of NTA - Powder | 25 | 18.9 | 17.7 | 11.4 | 15.2 |

This data shows that for most instances, no Prop 65 labeling should be required for FlexaTrac-NTA in typical I&I and consumer applications.

# *Other Health Effects*

Further study, conducted by internationally recognized scientific organizations, has shown that only after dosing FlexaTrac-NTA at exceedingly high concentrations are any harmful effects observed in test animals.[21,34,35]

In 1985 an in-depth study by Dr. Robert Anderson with support from Dr. George Becking (World Health Organization, Interregional Research Unit) was published. This study investigated FlexaTrac-NTA's human health safety and concluded that "FlexaTrac-NTA does not constitute a health risk to man as a result of its commercial use"[14] in detergent applications.

In 2008, an in vitro human skin dermal penetration study was conducted with radio-labeled FlexaTrac-NTA, to clarify if use with bare skin would result in an undue risk. This study showed in two exposure

levels (1000 and 4000 µg/cm$^2$) less than 0.1% of applied FlexaTrac-NTA was absorbed into the skin[36]. In general, a chemical needs to be lipophilic (soluble in oils) to penetrate skin at an appreciable level. FlexaTrac-NTA is not lipophilic, and the data from this study show that skin exposure to FlexaTrac-NTA should result in negligible risk.

This data history for acute and chronic effects is extensive, and cannot all be included here. These studies have shown:

- FlexaTrac-NTA can be a skin irritant in conditions where it is in skin contact for long periods of time. FlexaTrac-NTA is easily washed from the skin. When handling a formulated product containing FlexaTrac-NTA, it is likely that many substances present, including surfactants and antimicrobial additives may irritate the skin.
- FlexaTrac-NTA is practically non-toxic with dermal exposure. FlexaTrac-NTA has very low dermal penetration, and animal studies have shown that it does not penetrate the skin in sufficient enough amounts to cause toxicity.
- FlexaTrac-NTA can be an eye irritant. FlexaTrac-NTA can dissolve in the tear film on the surface of the eye, and can produce an irritant response (redness, watering).
- FlexaTrac-NTA is of low oral toxicity. Animal studies have shown FlexaTrac-NTA to have effects only at very high dose levels. In cleaning formulations, it is likely that other ingredients have much higher oral toxicity.
- FlexaTrac-NTA can be an inhalation irritant. As with any dust, inhalation of FlexaTrac-NTA can result in irritation of the nasal passages, throat and lungs. Coughing and sneezing may result. Animal studies have shown that temporary respiratory irritation ($RD_{50}$) is significant at 4.25 mg/L dust concentration
- FlexaTrac-NTA is of low inhalation toxicity. Acute animal studies have shown no toxic effects at up to 5 mg/m$^3$ FlexaTrac-NTA in air, while longer term studies in animals have shown shortness of breath as an effect.
- FlexaTrac-NTA is not a sensitizer (Dermal or Inhalation).
- FlexaTrac-NTA is not a mutagen (it does not alter DNA – It does not cause cancer via a mutagenic pathway). This has been shown in multiple tests.
- FlexaTrac-NTA has caused damage to the kidneys and urinary systems of test animals at long term, high dose exposures. These effects have never been seen in humans in occupational or consumer uses of FlexaTrac-NTA.
- FlexaTrac-NTA does not cause reproductive or developmental effects in animal studies.

## REACh Dossier for FlexaTrac-NTA – Human Health Effects

The most recent comprehensive review of FlexaTrac-NTA health effects occurred in 2010, in the preparation of the REACh dossier for FlexaTrac-NTA. All available data (through June 2010) was reviewed[37]. This comprehensive review contained hundreds of studies, and narrowed the available dataset down to the most scientifically valid studies. The following data was used for regulatory assessment:

## Acute Animal Toxicity, Sensitization and Corrosion Data

| Exposure Route | Type of Test | Species | Value |
|---|---|---|---|
| Oral | LD50 oral gavage | Wistar rat | 1300 mg/kg female, 1600 mg/kg male |

| | | | |
|---|---|---|---|
| Inhalation | LC50, 4 hour exposure | Albino rat | NOEL – 5.0 mg/l of air(maximum dose) |
| | LC50, 4 day exposure (6 hours per day) | Rats | NOEL – 2.0 mg/l of air |
| Dermal | Minimum Lethal Dose, 3 day exposure | New Zealand rabbit | > 10.000 mg/kg (no deaths) |
| Skin Irritation | Patch Tests of varying lengths | New Zealand rabbit | Slightly Irritating, based on multiple studies; non-corrosive |
| Eye Irritation | OECD 405 | Vienna White rabbit | Irritating to eyes |
| Respiratory Irritation | Alaire Test, 30 minute exposure | Wistar Rat | RD50 = 4.25 mg/l (estimate) |
| | | Mouse | Moderate at 1.09 mg/l, Severe at 7.6 mg/l |
| Skin Sensitization | Buehler Test | Guinea Pig | Not Sensitizing |
| | Closed Patch Test | Human Volunteers | Not Sensitizing |

## Repeat Dose/Chronic Toxicity Data

| Exposure Route | Type of Test | Species | Value |
|---|---|---|---|
| Repeat dose Oral: | 2 year feeding study | Rat | NOAEL = 92 mg/kg bw/day |
| | | | **Target organs affected** Kidneys, Urinary Tract |
| Repeat dose Dermal: | 28 and 91 day treatment, intact and abraded skin | New Zealand rabbit | NOAEL = 50 mg/kg bw/day mild skin irritation was observed |
| Repeat dose Inhalation: | Aerosol, 28 days, 6 hours per day, 5 days/week | Rat, Guinea Pig, Monkey | NOAEC = 0.21 mg/l (Rat, Monkey);<br>NOAEC = 0.34 mg/l (Guinea Pig) |

| Exposure Route | Type of Test | Species | Value |
|---|---|---|---|
| Mutagenicity – In Vitro | Ames Test (OECD 471), with and without metabolic activation | Salmonella | Negative |
| | Mammal cell gene mutation assay (OECD 476) | Mouse lymphoma L5178Y cells | Negative |
| Mutagenicity – In Vivo | Micronucleus Assay (OECD 474) | NMRI Mouse | Negative |
| Carcinogenicity | Oral, in feed, 104 weeks (equivalent to OECD 451) | Fischer 344 rat | NOAEL (Carcinogenicity) = 9.2 mg/kg bw/day;<br>LOAEL (Carcinogenicity) = 92 mg/kg bw/day<br>Effects - transitional cell hyperplasia and dysplasia of the renal pelvis, the ureter, and the urinary bladder<br>Classified as IARC 2B, DSD R40, CLP H351 |

| | | | |
|---|---|---|---|
| | Oral, drinking water, 703 days (equivalent to OECD 451) | Sprague-Dawley Rat | LOAEL (Carcinogenicity) = 100 mg/kg bw/day increased tumor incidence<br>Classified as IARC 2B, DSD R40, CLP H351 |
| | Oral, in feed, 18 months (equivalent to OECD 451) | B6C3F1 Mouse, Fischer 344 Rat) | Neoplastic effects: yes (Rats: neoploasms of kidney and ureter; Mice: Neoplasms of urinary tract)<br>Classified as IARC 2B, DSD R40, CLP H351 |
| Reproductive and developmental toxicity | Oral, in feed, 2 generation (equivalent to OECD 416) | rat | NOAEL (reproduction) (F0, F1): 450 mg/kg bw/day (nominal) (male/female) (overall effects)<br>NOEL (systemic) (all): 90 mg/kg bw/day (nominal) (male/female) (overall effect)<br>LOAEL (systemic) (F0, F1): 450 mg/kg bw/day (nominal) (male/female) (depressed body weight gain) |
| Developmental toxicity (Teratogenicity) | Oral, gavage, dosing during gestation days 7-16 (equivalent to OECD 414) | New Zealand rabbit | NOAEL (teratogenicity): 250 mg/kg bw/day (actual dose received) (overall effect on fetuses) |

The REACh Risk Assessment process requires that Derived No Effect Levels (DNEL's) be calculated for likely exposure routes. These must be derived for occupational and general population exposures. It was determined that the most critical route of exposure to FlexaTrac-NTA is the inhalation of the powder, or formulations containing the powdered FlexaTrac-NTA as an ingredient. These values were derived from the available best data, and by using ECHA's methodology for risk assessment. The value shown is a value which should be seen as a ceiling for FlexaTrac-NTA exposure level. General population values are 4X lower due to an additional safety factor.

| Exposure pattern | DNEL | |
|---|---|---|
| | Workers | General population |
| Acute – inhalation, systemic effects | 9.6 mg/m$^3$ | 2.4 mg/m$^3$ |
| Acute – oral, systemic effects | n.a. | 0.9 mg/kg/d |
| Long-term – inhalation, systemic effects | 3.2 mg/m$^3$ | 0.8 mg/m$^3$ |
| Long-term – oral, systemic effects | n.a. | 0.3 mg/kg/d |

## REACh Exposure Scenarios and Proof of Safe Use

Within REACh, once the DNEL's are calculated, a registrant must prove that the uses of the substance result in exposures which are less than the DNEL. In 25 different exposure scenarios, using data provided by downstream users, safe use was proven for each condition. The typical end uses for FlexaTrac-NTA were covered; please see Ascend's Extended Safety Data Sheet for details[38].

## *Health Effects Conclusions*

In-depth reviews on FlexaTrac-NTA's human health safety have been conducted. FlexaTrac-NTA, in fact, is one of the most extensively studied chemicals known to man. Organizations such as the European Commission, California Environmental Protection Agency, World Health Organization, United Nations, U.S. Environmental Protection Agency, Universities Associated with Research and Education in Pathology, and many others have studied the effects of FlexaTrac-NTA on people and have concluded that FlexaTrac-NTA is safe on the basis of anticipated use and exposure patterns.


# *FlexaTrac-NTA*

## Environmental Profile

## *Details on Environmental Effects*

Extensive studies since the 1970's have shown that FlexaTrac-NTA is safe for the environment, and is in fact preferable to other chelants (such as EDTA, and Phosphates/phosphonates). As with Human Health, FlexaTrac-NTA's Environmental Toxicity was thoroughly reviewed during the 2010 REACh registration. Risk assessment of typical FlexaTrac-NTA uses, in accordance to the strict criteria of the European Chemicals Agency, showed that all uses were allowable, and resulted in no excess risk to the environment[37].

In 1980, the US Environmental Protection Agency conducted a quantitative (where possible) and qualitative assessment of risk to human health and the environment of FlexaTrac-NTA and concluded; at the low expected environmental concentrations, no adverse environmental effects are anticipated.[11]

### Biodegradation

FlexaTrac-NTA is rapidly biodegradable in aerobic, anaerobic, freshwater and marine conditions in the environment[4,26,39,40,41,42,43,44]. FlexaTrac-NTA can also undergo both photo- and chemical- degradation. When broken down, FlexaTrac-NTA is converted into carbon dioxide, water and inorganic nitrogen by microorganisms present in the environment. Microbial degradation is complete; FlexaTrac-NTA and intermediate compounds which are formed during the FlexaTrac-NTA degradation reaction do not persist in the environment[45].

In addition, studies have repeatedly shown that FlexaTrac-NTA metal complexes are rapidly biodegraded in the environment[46,47,48,49,50,51]. FlexaTrac-NTA-degrading organisms will destabilize the metal-FlexaTrac-NTA complex in the environment which would act to limit mobilization of metals as soluble FlexaTrac-NTA chelates. Metal mobilization is addressed in detail below.

FlexaTrac-NTA is not only broken down aerobically, it is also broken down in anaerobic environments such as septic tanks. Studies have demonstrated that properly functioning septic tank systems effectively remove FlexaTrac-NTA.[52]

FlexaTrac-NTA is biodegradable under marine and estuarine conditions. The degradation rate of FlexaTrac-NTA has been shown to decrease with increasing salinity; however, researchers have concluded that the restricted FlexaTrac-NTA biodegradation in saline waters is probably caused by the low concentration of bacteria in saline waters rather than by the inherent nature of FlexaTrac-NTA[4].

Due to its rapid biodegradation, products containing FlexaTrac-NTA may be eligible for a General Environmental Benefit Claim under US rules, with regard to biodegradation[53]. While the whole formulation should be taken into account, FlexaTrac-NTA would not prevent such a claim from being made. Due to its high level of effectiveness, FlexaTrac-NTA containing products may also benefit from a claim of benefit due to effectiveness, since it is possible that effective cleaning may be performed with lower use levels.

In recognition of FlexaTrac-NTA's positive environmental profile, Canada allows the use of FlexaTrac-NTA in Ecologo certified products. Ecologo is a long established certification system for environmentally preferable products, and allows FlexaTrac-NTA use in products in Commercial Car Washes (5% FlexaTrac-

NTA use level), and also Laundry Detergents (13.5 grams FlexaTrac-NTA per detergent dose use level)[27,28].

Available Biodegradation Data is summarized below[37]

| Type of Study | Method | Duration [d] | Inoculum[1)] | $Na_3$FlexaTrac-NTA conc. [mg/l] | Degradation [%] | Lag phase [d] |
|---|---|---|---|---|---|---|
| Modified OECD Screening Test | OECD 301 E | 14 | River water | 70 | 100 | 5 |
| Modified OECD Screening Test | OECD 301 E | 14 | Industrial WWTP effluent | 70 | 100 | 5-11 |
| Modified OECD Screening Test | OECD 301 E | 7 | Adapted AS | 70 | 100 | 1 |
| Modified OECD Screening Test | OECD 301 E | 12 | Adapted AS | 140 | 75-90 | 2-5 |
| Sturm Test | $CO_2$ evol. | 9 | Effluent from stand test | 10/20 | 100 | - |
| Manometric Respirometry Test | OECD 301 F | 28 | Industrial AS | 250-360 | 92 | 16 |
| Combined CO 2 /DOC Test | Other | 28 | Industrial AS | 140 | > 95 (DOC)<br>91 ($CO_2$) | 2 (DOC)<br>5 ($CO_2$) |
| Modified Zahn-Wellens Test | OECD 302 B | 28 | Industrial AS | 1400 | 96 | 7 |
| Die-away Test | Other | 23 | Municipal AS | 210 | 100 | 14 |

## Metal Mobilization

FlexaTrac-NTA is very efficient at chelating heavy metals which has prompted discussion over FlexaTrac-NTA's ability to mobilize heavy metals from wastewater sludge or river sediment. Research has indicated, however, that FlexaTrac-NTA does not cause remobilization of heavy metals from wastewater sludge or river sediment and does not aid in the migration of heavy metals in the environment[4,11,14,31]. FlexaTrac-NTA and FlexaTrac-NTA-metal complexes are rapidly and efficiently biodegraded thus reducing FlexaTrac-NTA's resulting impact on metal remobilization. These results are confirmed by numerous studies including most recently a four year analysis[54].

The four-year study mentioned above, did not identify any significant changes in the concentrations of lead, cadmium, chromium, iron, copper, manganese and zinc in the overflow from sewage treatment plants receiving FlexaTrac-NTA in their influent water. A slight increase in nickel was noted, but no detrimental effects on water quality can be implied.

## Aquatic Toxicity

The acute and chronic toxicity of FlexaTrac-NTA to aquatic organisms has been extensively studied. It has been concluded that FlexaTrac-NTA would not adversely affect freshwater or marine organisms. A two year field study gave no evidence that FlexaTrac-NTA promotes long term growth of algae up to 500ug/L[55,56]. No toxic effects were observed in any of the many species that were studied, including fish. In shorter, controlled laboratory studies of FlexaTrac-NTA, FlexaTrac-NTA shows a toxic dose to fish and invertebrate species which is well above levels seen in the environment[57,58,59,60] . Because of this, FlexaTrac-NTA does not require an ecotoxicity label under the GHS system. This data is discussed below in the REACh registration section.

An often misunderstood aspect of chelant toxicity is the effects of chelants on algae. In controlled lab studies, it is often seen that chelants such as FlexaTrac-NTA, EDTA and other show toxic effects to algae. These effects are not seen, however, in real world conditions and model stream systems[55,61].

In lab studies, the toxicity of FlexaTrac-NTA (and most other chelants) to algae is due to metal starvation. Metals which are necessary for the metabolism in algae are chelated, and are not biologically available to the algae. Normal function is impaired, and the algae cannot survive. In the 2007 EU Risk Assessment Report for the European Union[61], the BAuA (German risk assessment body) determined that the effects seen in lab studies cannot be used for risk assessment, because in a real world environment excess metals on water would remain available for the algae. Similar language and reasoning is present in other EU Risk Assessments.[62]

## Wastewater Treatment Facilities

The behavior of FlexaTrac-NTA in wastewater treatment facilities has been thoroughly investigated. Research has concluded that FlexaTrac-NTA does not adversely affect the wastewater treatment process. FlexaTrac-NTA may be efficiently treated in aerobic[63,64,65] and septic[52,66,67] waste treatment. Studies have shown that downstream of an effective wastewater treatment system, any small amount of FlexaTrac-NTA which remains is degraded in the receiving water, and does not measurably contribute to a decline in water quality. [68]

In Germany, specific language in German wastewater regulations[69] allows the use of FlexaTrac-NTA in many types of products. While the regulation should be consulted for specific cases, in general it requires that organic complexing agents, such as FlexaTrac-NTA, should be more than 80% biodegradable in a 28 day biodegradation study. FlexaTrac-NTA meets this requirement.

## Terrestrial Plant Toxicity

The effects of FlexaTrac-NTA on land plants have been studied, but not as extensively as the effects on aquatic plants. To Ascend's knowledge no prohibitions exist for the use of FlexaTrac-NTA in soil treatment formulations, but the customer should evaluate the health and safety risks of such uses.

In a 1974 study[70] FlexaTrac-NTA was applied to two different plant speies. Bush Beans were exposed to trisodium FlexaTrac-NTA in soil at up to 2500 ppm (0.25%), and Soybeans were exposed to up to 1000 ppm (0.1%) in soil. The Bush Bean study showed slightly decreased yield at the highest dose level, and a dose dependent increase in the concentration of metals in the stems and leaves of these plants. It was not determined if these two effects were related. The Soybean study showed no difference in yield, but also showed dose dependent increases in metals content in the plants.

Cooper et al (1999)[71] reported the effectiveness of various chelants on the extraction of lead from contaminated soil. Of the chelants tested FlexaTrac-NTA had the lowest rate of extraction of lead from the soil. It is not known if this is due to the rapid biodegradation of FlexaTrac-NTA, lack of affinity of the tested plant species for FlexaTrac-NTA complexes or due to lack of affinity of FlexaTrac-NTA for lead under the tested conditions.

FlexaTrac-NTA was also evaluated for effects on Mustard Greens grown in soils which contain excess cadmium[72]. This 2006 study showed that FlexaTrac-NTA soil treatment increased plant uptake of cadmium and also in an increased production of antioxidant chemicals (phenolics and other organic acids) within the plants.

Borowiec et al (2009)[73] reported that FlexaTrac-NTA is more easily biodegraded than EDTA or GLDA. This study focused on chelants which are used in liquid fertilizer for delivery of micronutrients.

## REACh Dossier for FlexaTrac-NTA – Environmental Health Effects

In preparation of the dossier for FlexaTrac-NTA's REACh registration, all available data (through June 2010) was reviewed[37]. This comprehensive review contained hundreds of studies, and narrowed the available dataset down to the most scientifically valid studies. The following data was used for regulatory assessment:

## Aquatic Toxicity

| Test Category | Test Description | Species | Result |
|---|---|---|---|
| Fish, Short Term | TL50, Fresh water, flow through, 96 hour. | Pimephales promelas | 103 mg/l |
| | TL50, Fresh water, flow through, 96 hour (similar to OECD 203) | Lepomis macrochirus | Soft Water - 298 mg/l<br>Hard Water = 510 mg/l |
| Fish, Long Term | Fresh water, flow through, 229 days (similar to US-EPA 72-5) | Pimephales promelas | NOEC (229 d): > 54 mg/L, based on: mortality, reproduction (spawning activity and hatchability)<br>NOEC (30 d): > 60.2 mg/L test mat. (meas. (arithm. mean)) based on: growth |
| | LC50, Fresh water, flow through, 27 days embryo-larval test | Oncorhynchus mykiss | Water Hardness 50 mg/l – LC50 = 90.5 mg/l<br>Water Hardness 200 mg/l – LC50 =114 mg/l |

| | | | |
|---|---|---|---|
| Aquatic Invertebrates, Short Term | TL50, Fresh water, flow through, 96 hour APHA Standard Method | Gammarus pseudolimnaeus | 80 mg/L, based on: mortality |
| | LC50 and EC50, Fresh water, static, 48 hour (similar to OECD Guideline 202) | Daphnia magna | L(E)C50 560 mg/L, based on: mortality, immobility |
| | TL50, Fresh water, static, 96 hour | Physa heterostropha | 400 mg/L, based on: mortality |
| Aquatic Invertebrates, Long Term | NOEC, Fresh water, flow through, 21 weeks | Gammarus psuedolimnaeus | 9.3 mg/L for survival<br>18.7 mg/L for reproduction |
| | NOEC, Fresh water, semi-static, 21 day | Daphnia magna | 100 mg/L based on: mortality |
| | NOEC, Fresh water, flow through, 120 days | Helisoma trivolvis | 12.5 mg/l based on: growth |
| Algae and Aquatic Plants, Long Term | EC50/NOEC, Freshwater, Static, 72 hour (OECD 201) | Desmodesmus subspicatus | EC50 (72 h): > 91.5 mg/l<br>NOEC (72 h): 1.43 mg/l<br>EC10 (72 h): 22.8 mg/l based on: biomass<br>EC10 (72 h): 74.8 mg/l based on: growth rate |
| | EC50, Freshwater, Static and flow-through, 5 days (Equivalent to OECD 201) | Navicula seminulum | flowthrough, soft water = 143 mg/l<br>static, soft water = 198 mg/l<br>flowthrough, hard water = 507 mg/l<br>static, hard water = 507 mg/l |
| Biodegradation | Multiple valid studies show degradation of 75-100% within 7-28 days. Classified as "Readily biodegradable", in all environmental compartments, even at low environmental temperatures. | | |
| Bioaccumulative potential | Not expected to bioaccumulate. | | |

The REACh Risk Assessment process requires that Predicted No Effect Concentrations (PNEC's) be calculated for likely exposure routes. These values were derived from the available best data, and by using ECHA's methodology for risk assessment.

| Exposure pattern | PNEC |
|---|---|
| PNEC aqua (freshwater) | 0.93 mg/L |
| PNEC aqua (marine water) | 0.093 mg/L |
| PNEC aqua (intermittent releases) | 0.8 mg/L |
| Freshwater Sediment | No exposure of sediment expected |
| Marine Sediment | No exposure of sediment expected |
| Soil | No exposure of soil expected |
| PNEC STP | 270 mg/L |
| PNEC (oral, secondary poisoning) | No potential for bioaccumulation |

### REACh Exposure Scenarios and Proof of Safe Use

Within REACh, once the PNEC's are calculated, a registrant must prove that the uses of the substance result in exposures which are less than the PNEC. In 25 different exposure scenarios, using data provided by downstream users, safe use was proven for each condition. The typical end uses for FlexaTrac-NTA were covered; please see Ascend's Extended Safety Data Sheet for details[38].

## *Environmental Conclusions*

In-depth reviews on FlexaTrac-NTA's environmental health safety have been conducted. FlexaTrac-NTA, in fact, is one of the most extensively studied chemicals known to man. Organizations such as the World Health Organization, United Nations, U.S. Environmental Protection Agency, Universities Associated with Research and Education in Pathology, Great Lakes Research Advisory Group (International Joint Commission), German Environment Ministry and many others have studied the effects of FlexaTrac-NTA on the environment and have concluded that FlexaTrac-NTA is safe on the basis of anticipated use and exposure patterns.


## *FlexaTrac-NTA*

**Physical and Chemical Properties**

# *Details on Physical and Chemical Properties*

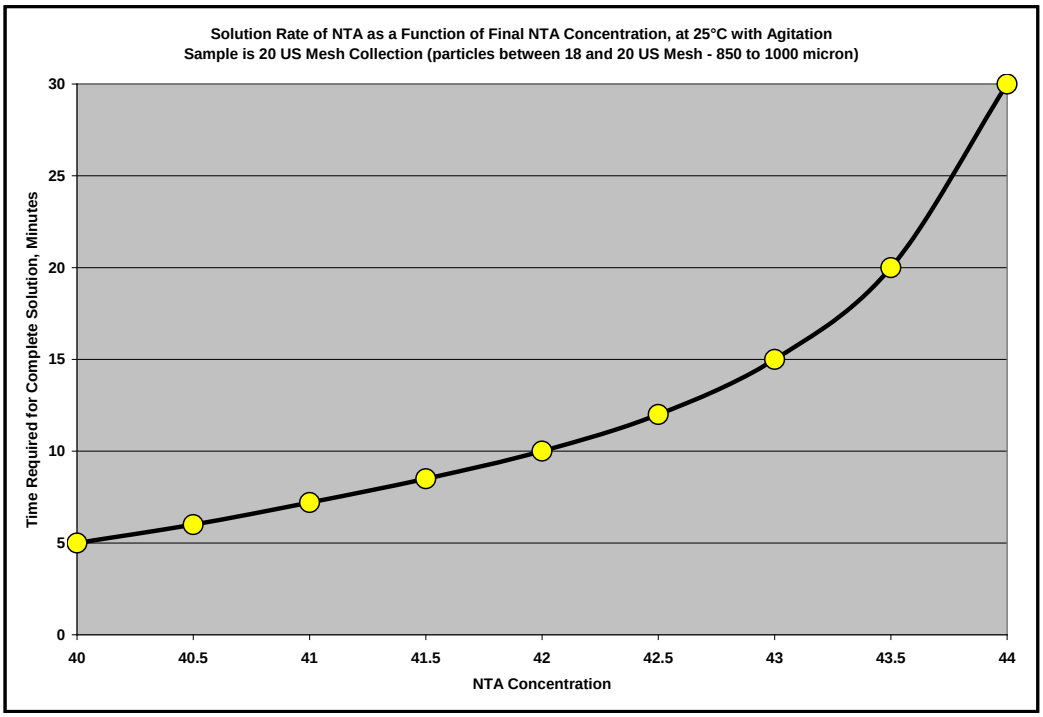
FlexaTrac-NTA, whether in powder or solution forms, offers a number of properties which allow for easy handling, storage and use. The data provided below is considered typical of Ascend FlexaTrac-NTA, and summaries of this data are provided on the Ascend Extended Safety Data Sheet. The source for this data is internal Ascend technical reports unless otherwise noted.

## Water Solubility

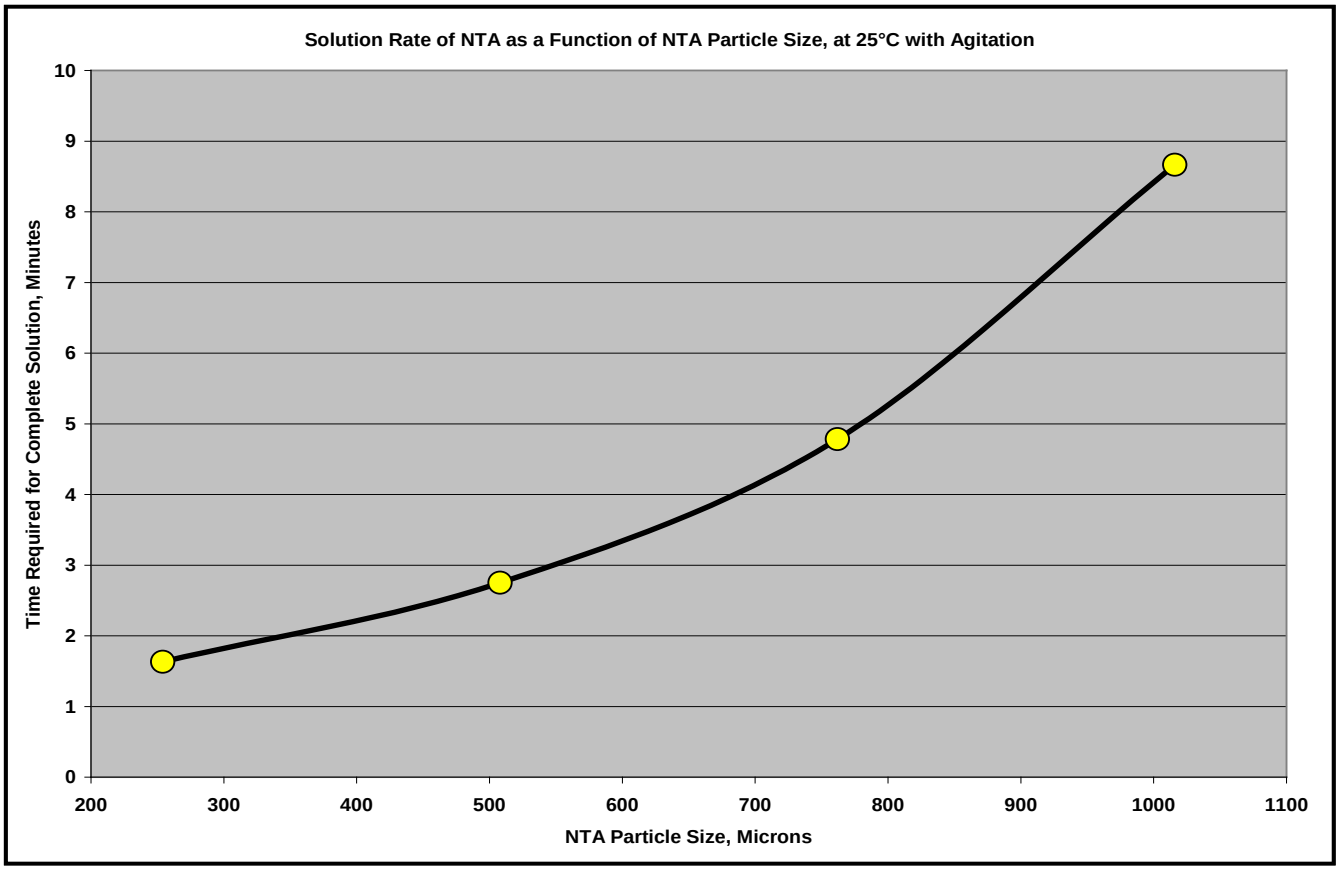
FlexaTrac-NTA powder is very water soluble. At 20°C, the solubility of FlexaTrac-NTA in water is 457grams of FlexaTrac-NTA/liter of solution. The solubility of FlexaTrac-NTA is directly related to temperature; FlexaTrac-NTA's solubility increases linearly with increasing temperature. At 100°C, the water solubility of FlexaTrac-NTA is 530 grams of FlexaTrac-NTA/liter of solution. The presence of other solutes in a formulated product may affect the ultimate solubility of FlexaTrac-NTA in a formulation.

As with most salts, FlexaTrac-NTA dissolves over a period of time. The time required for FlexaTrac-NTA to dissolve increases with FlexaTrac-NTA concentration, and the particle size of the FlexaTrac-NTA particles. This time decreases with solution temperature and the rate of agitation. As the concentration of a solution of FlexaTrac-NTA increases, more work (agitation, time) must be done to get material into solution. As particle size increases, there is less surface area per weight of FlexaTrac-NTA. This results in a smaller amount of active surface where dissolution can take place.

As can be seen from the data presented below, the curve of concentration dependent solution rate flattens at lower concentrations. At typical use levels, FlexaTrac-NTA should dissolve quickly.



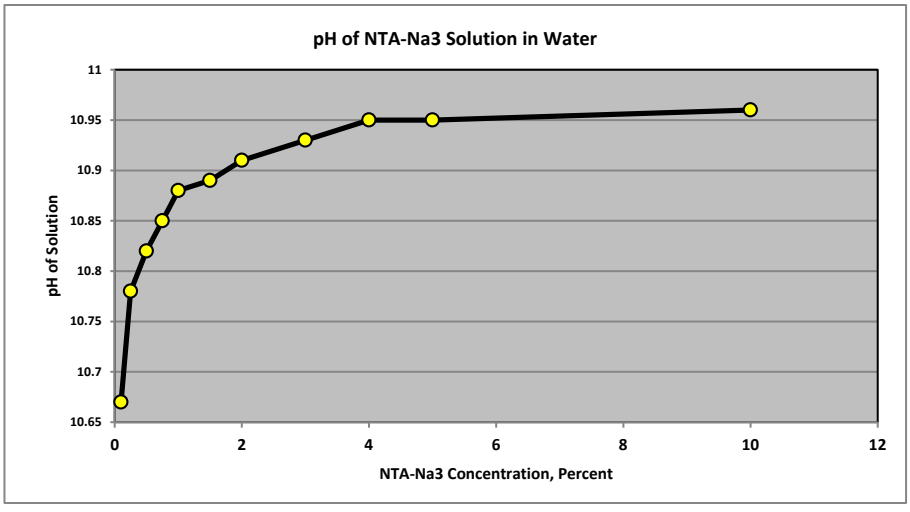
The particle size dependent graph below shows the dissolution rate of FlexaTrac-NTA in water, which varies considerably with increasing particle size. Since FlexaTrac-NTA as supplied will always be a range of particle sizes, it can be assumed the last particles of FlexaTrac-NTA to dissolve are the larger ones present, which require additional work to dissolve. This should not be indicative of insoluble material.




## pH of Solution

When FlexaTrac-NTA is dissolved in water the resulting solution is basic. The pH of various solutions of FlexaTrac-NTA in water is shown below.

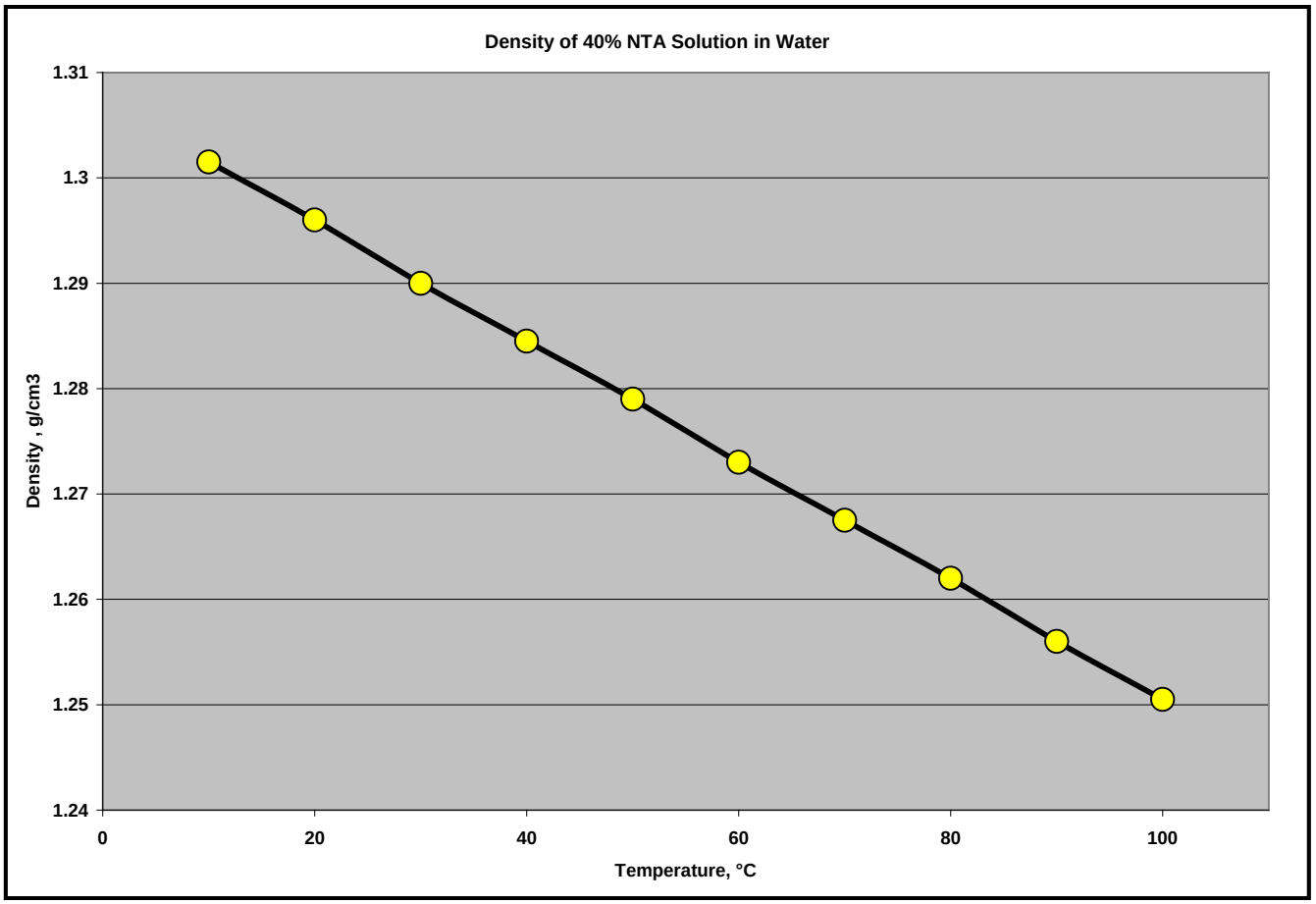
| FlexaTrac-NTA Concentration in Water | pH of Solution |
|---|---|
| 0.1 | 10.67 |
| 0.25 | 10.78 |
| 0.5 | 10.82 |
| 0.75 | 10.85 |
| 1.0 | 10.88 |
| 1.5 | 10.89 |
| 2.0 | 10.91 |
| 3.0 | 10.93 |
| 4.0 | 10.95 |
| 5.0 | 10.95 |
| 10.0 | 10.96 |



## Density

The crystalline density of FlexaTrac-NTA powder, as well as the bulk density of FlexaTrac-NTA powder has been measured. As a pure crystal, the density of FlexaTrac-NTA has been measured as 1.77 g/cm$^3$. Since FlexaTrac-NTA is sold as a powder, in bulk form the density of FlexaTrac-NTA includes the density contribution of the entrained air. The Bulk Density of FlexaTrac-NTA powder is 0.65-0.78 g/cm$^3$ at 25°C.

FlexaTrac-NTA solution's density will vary linearly with temperature.

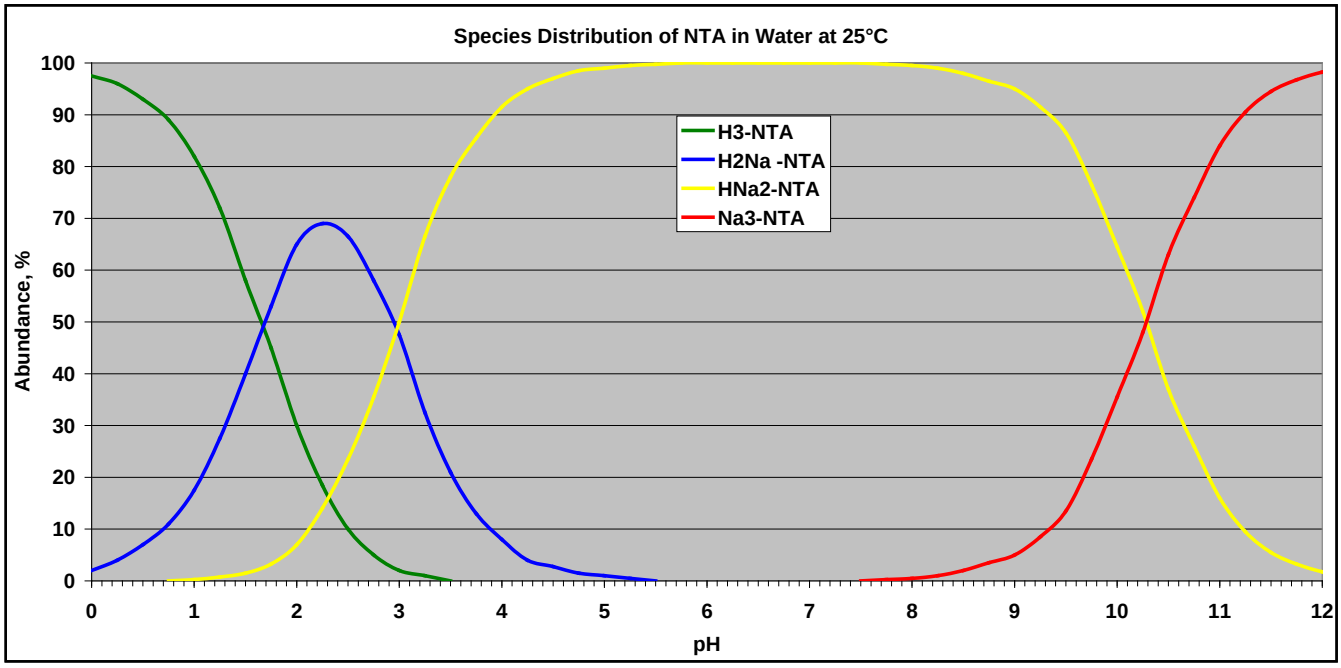



## Partition Coefficient

The partition Coefficient was calculated to be between -2.62 (low pH) and -13.2 (high pH) at 25°C[74]. These values show that in mixed oil and water environment, the FlexaTrac-NTA should stay in the water portion. The pH dependency of this value show that at lower pH (pH = 3.5 or less), some FlexaTrac-NTA will dissolve into oil, but at slightly acid to basic pH (pH = 3.5 or higher), essentially all of the FlexaTrac-NTA will remain in the water portion of the mixture.

## FlexaTrac-NTA Speciation in Water Solutions

When Ascend's FlexaTrac-NTA is dissolved in water, it forms a solution of Sodium FlexaTrac-NTA, at a high pH (10-11). As the pH of that solution is adjusted, various forms of FlexaTrac-NTA may be present. These pH dependent forms are the result of protons (hydrogen ions) associating with the acetate groups. As the level of protons increases with decreasing pH, these associations are more common. The data shown below is for an ideal solution of FlexaTrac-NTA in water, with no other metals present.



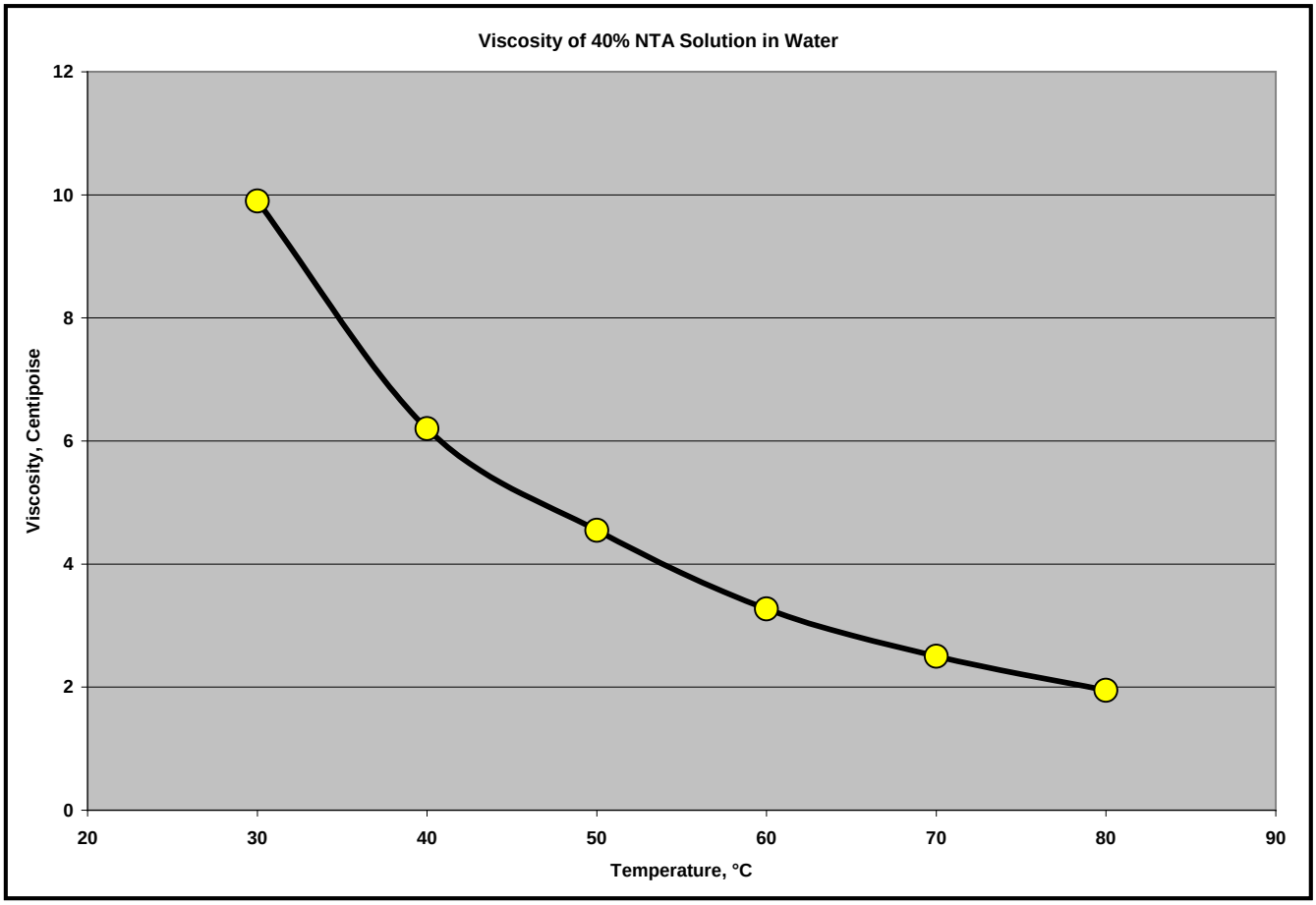

## Vapor Pressure

No accurate vapor pressures have been measured on FlexaTrac-NTA. Structurally FlexaTrac-NTA should not evaporate at relevant temperatures. Since it is a hydrate, there is always water vapor present in the air above a sample of FlexaTrac-NTA. Calculation of vapor pressure has resulted in a value of 0.000000001 hPa at 25°C. FlexaTrac-NTA will not contribute to VOC emissions from facilities or from formulated products.

## Viscosity

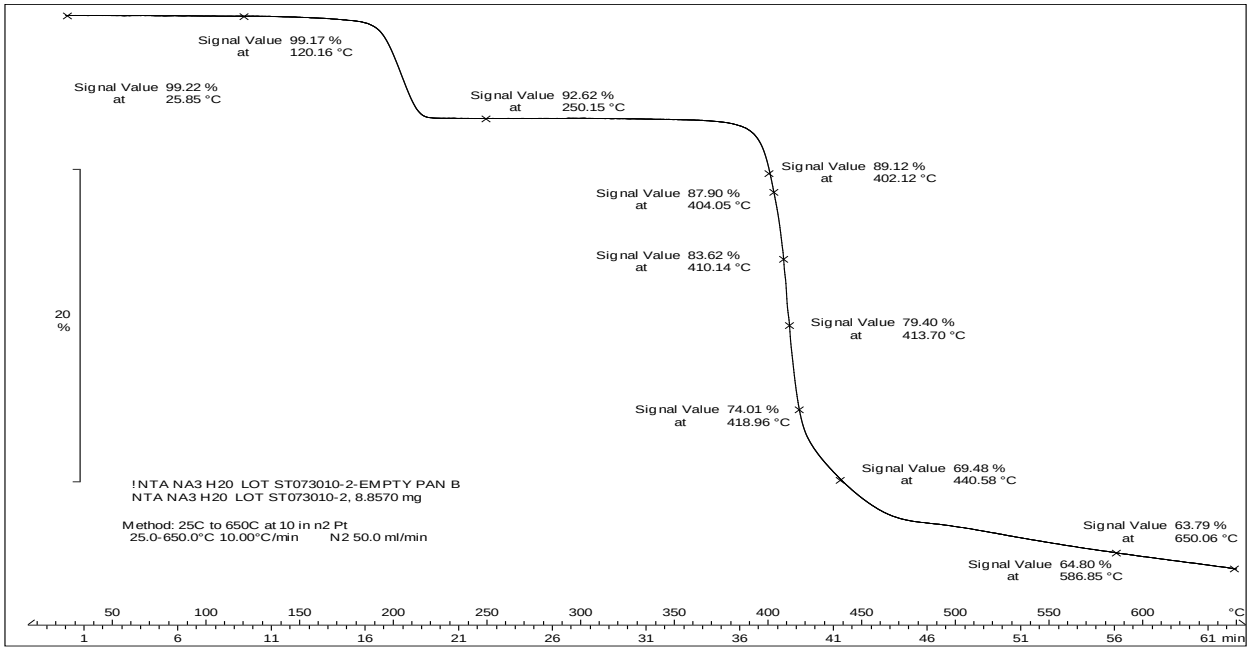
FlexaTrac-NTA solutions will have a viscosity which varies with both temperature and concentration. As concentration increases, viscosity will increase. As temperature increases, viscosity will decrease. The data presented below is for 40% FlexaTrac-NTA solution in water. Extrapolation of this data back to 20°C and 10°C reveals viscosities which are still low – 19 centipoise at 20°C and 60 centipoise at 10°C. These values show that even at lower temperatures, FlexaTrac-NTA solution would be easily handled.

Lower concentrations of FlexaTrac-NTA in water would have a viscosity curve shifted to the left, to lower viscosities at a given temperature.



## Melt (Degradation) Point

FlexaTrac-NTA does not melt. As temperature is increased, several transitions occur. Since FlexaTrac-NTA is a hydrate, the first transition involves the release of the water bound to the FlexaTrac-NTA. This occurs over a broad range, from 120 to 215°C. As temperature further increases, FlexaTrac-NTA will degrade into smaller molecules. This degradation begins slowly at 340°C, and rapidly from 390 to 421°C. Below is data from a Thermogravimetric analysis of FlexaTrac-NTA, showing this behavior. At the end of this heating process, the remaining material is a black char of carbon and sodium salts.




Thermogravimetric analysis (TGA) of Ascend FlexaTrac-NTA powder

Weight Loss Percentage During TGA

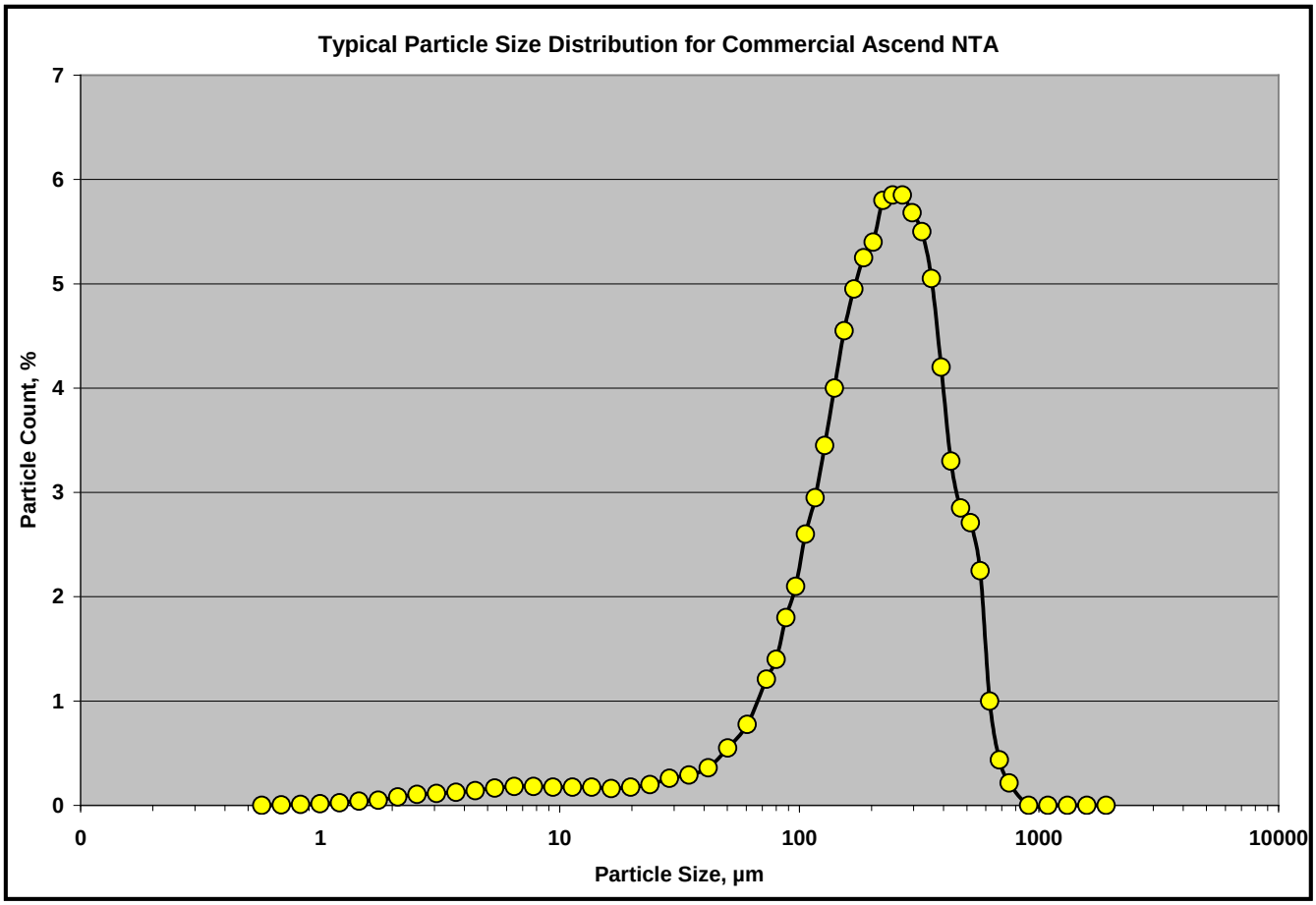
| | **Start condition = dry at 120°C** | | **Start condition = dehydrated at 250°C** |
|---|---|---|---|
| **% weight lost** | **Temperature, °C** | **% weight lost** | **Temperature, °C** |
| 6.55 | 250 | 5 | 404 |
| 10 | 402 | 10 | 410 |
| 20 | 414 | 20 | 419 |
| 30 | 441 | 30 | 587 |
| 36 | 650 | 31 | 650 |

## Rehydration

FlexaTrac-NTA powder is sold as a monohydrate; every molecule of FlexaTrac-NTA is hydrogen bonded to a molecule of water. This is the natural state of FlexaTrac-NTA powder. In this hydrated form, FlexaTrac-NTA will remain a free flowing material, and may be shipped, stored and used worldwide. If FlexaTrac-NTA powder is heated to dryness, and allowed to cool, it will regain moisture from the atmosphere. The rate of this moisture regain is proportional to the humidity.

## Particle Size Distribution

Data for typical commercial FlexaTrac-NTA is below. FlexaTrac-NTA particle size can be affected by conveying systems, as larger particles may be abraded in aggressive handling systems.




## Flashpoint

FlexaTrac-NTA is non-flammable and non-combustible, and does not have a Flashpoint.

## Dust Explosivity

FlexaTrac-NTA powder is practically non-explosive. Several studies have shown only one explosion, as an FlexaTrac-NTA dust concentration of more than 2 kilograms per cubic meter ($kg/m^3$). This is a blizzard of FlexaTrac-NTA, and cannot be sustained in standard handling. Other studies from industry have shown that explosions cannot occur at dust concentrations of less than 1 $kg/m^3$.


## *FlexaTrac-NTA*

**Worker and Environmental Protections**

As with any chemical product, proper care must be taken to handle FlexaTrac-NTA. Whether in expensive automated conveying systems or in small one-bag-at-a-time operations, proper use of Engineering Controls, Work Practices and Personal Protective Equipment will minimize or eliminate both worker exposure to FlexaTrac-NTA and release of FlexaTrac-NTA to the environment. As mentioned in the Human Health and Environmental portions of this document, multiple government and academic agencies and institutions have concluded that consumer and industrial use of FlexaTrac-NTA is safe; however the measures detailed here will contribute to a safe and healthy workplace.

# *Engineering Controls*

Proper engineering of a facility is the first step to exposure reduction and elimination. While some engineering solutions require substantial time, effort and money, small incremental changes in handling systems can yield large benefits to worker and environmental safety and health.

## Dust Control

Control of dust from FlexaTrac-NTA powder is essential to a clean and safe workplace. Any dust generating material, if not properly controlled, can contribute to health (respiratory irritation) and safety (slip/fall) hazards. Valves and dispensing systems should be constructed to contain particles. This is especially important with slide gate valves and dumping systems.

Proper ventilation can reduce the amount of dust in the air. Air circulation should carry any dusts, including FlexaTrac-NTA, away from workers to a filtration system. Installation of Local Exhaust Ventilation (LEV) at particular dust “hot spots” can greatly reduce the overall presence of dust in a work area.

## Spill Prevention

Spills of both FlexaTrac-NTA powder and Solution should be minimized, and cleaned up quickly. A spill of FlexaTrac-NTA powder onto a wet surface can create a slip hazard. Equipment should be designed to provide containment of FlexaTrac-NTA and related materials.

## Conveying Systems

FlexaTrac-NTA Powder conveying systems, whether mechanical or pneumatic, should be constructed to minimize clogs due to compaction or bridging. Fewer clogs mean lower exposure for maintenance staff. Air exhausts from pneumatic systems should include a filtration system.

Pumping and piping systems for FlexaTrac-NTA solution should be designed with drain points, to allow proper clearing of the system prior to any maintenance work. FlexaTrac-NTA solution should function well in systems typical for low viscosity fluids.

# *Work Practices*

Coupled with Engineering, workplace methods and procedures can reduce chemical exposure, lessen chances for stress or strain injury and improve workplace efficiency.

## Training

In most world areas it is legally required to educate workers in the properties, hazards and risks of working with chemical products. In addition to any mandated training, workers should be educated in proper workplace hygiene, including product containment. Care should be taken to keep chemicals in the chemical handling area, and away from eating/break areas. Establishment of area rules and procedures will serve to reduce overall exposure to any chemicals in the facility, including FlexaTrac-NTA.

Ascend provides FlexaTrac-NTA in variety of packaging. For small packaging (50 pound or 25 kilogram bags), workplace training should include proper lifting, carrying and opening techniques. Larger packages for both powder and solution (totes, supersacks, railcars) are also available. Proper training for these should include safe use of lifting and moving equipment, as well as proper connection to product conveying and use systems.

## Monitoring

It is important to know the level of FlexaTrac-NTA to which workers are exposed. While there is no government derived workplace standard for FlexaTrac-NTA, Ascend has used ACGIH methods to derive a workplace guideline of 1 mg/m$^3$ as an 8 hour TWA, and 2 mg/m$^3$ as a Short Term Exposure Limit. In 2010, using the European Chemicals Bureau's methods for DNEL calculation, Ascend derived a no-effect (safe exposure) workplace level of 3.2 mg/m$^3$. While there are chemical specific tests for FlexaTrac-NTA, an economical screening method to determine exposure level could start with a simple total dust collection. If the dust level were to exceed 1 mg/m$^3$, more specific testing could be conducted.

## Rotation

Concerns about FlexaTrac-NTA exposure or repetitive strain from FlexaTrac-NTA packing handling can be reduced through job rotation. The overall work day exposure can be reduced by periodically moving workers from the FlexaTrac-NTA facility. This practice also contributes to a broadly trained workforce, allowing more flexibility in operations.

## Hygiene

Establishment of proper workplace hygiene practices is key to keeping FlexaTrac-NTA where it is supposed to be. Work uniforms, designated eating areas, garment changing areas, laundry and personal washing procedures will serve to contain a variety of chemicals, including FlexaTrac-NTA.

# *Personal Protective Equipment*

The last line of defense for worker protection is the proper use of personal protective equipment. Engineering and administrative controls should come first, because failure to properly use and maintain PPE, in an uncontrolled environment, results in an immediate exposure to a hazard.

## Eye and Face Protection

Any dust can irritate the eyes. Ascend recommends goggles for eye protection, as safety glasses rarely offer dust protection. Workers near pressurized systems containing FlexaTrac-NTA solution should consider goggles and face shields.

## Respiratory Protection

Any workplace which handles powders should consider the need to respiratory protection. The use of a NIOSH N95 or higher particulate mask will offer a high degree of protection. Local and national rules/legislation should be consulted to determine rules governing respiratory protection programs.

## Skin Protection

FlexaTrac-NTA can irritate skin, if in contact for extended periods of time. Work uniforms suited to the work environment offer protection to the body. Long sleeve shirts and long pants can be worn in lieu of coveralls. Leather gloves and any polymer gloves offer sufficient hand protection, but should be selected in consideration of work tasks (package handling, valve manipulation, etc). FlexaTrac-NTA solution should not penetrate polymer gloves, but exposure to surfactants or other chemicals in a formulation containing FlexaTrac-NTA could compromise gloves.


## *FlexaTrac-NTA*

**GHS, HMIS and NFPA Hazard Rankings**

FlexaTrac-NTA is classified as hazardous under the Global Harmonized System of Hazard Communication (GHS). The GHS is a United Nations system for accurately communicating the hazards of chemical substances and mixtures, and is currently on its fifth revision[75]. The basis for the classifications is discussed in the various sections above. Under the Global Harmonized Standard for Hazard Communication (GHS), Version 5, FlexaTrac-NTA is classified as follows:

| Category | Sub-Category | Classification |
|---|---|---|
| Physical Hazards | | Not classified for any physical hazard |
| Acute Health Hazards | Acute Toxicity, Oral | Category 4, Harmful if swallowed |
| | Serious Eye Irritation/ Eye Damage | Category 2, Causes serious eye irritation. |
| Chronic Health Hazards | Carcinogenicity | Category 2, Suspected of causing cancer |
| Specific Target Organ Toxicity (STOT), Acute Exposure | | Not classified for any specific organ hazard |
| Acute Environmental Hazards | Toxicity to Algae | Category 3, Harmful to Aquatic Life |
| Long-term Environmental Hazards | | Not classified for any long term environmental hazard |
| Signal Word | Warning | |
| Pictogram |  | |

Under the 3rd revision of the HMIS[76] and the 2012 NFPA 704 standard[77], FlexaTrac-NTA is rated as follows:

| HMIS III | Rating | Basis for Classification |
|---|---|---|
| Health | 1* | Serious Eye Irritation (GHS Category 2), Oral toxicity; Carcinogenicity |
| Flammability | 0 | No known effects |
| Physical Hazard | 0 | No known effects |
| Personal Protection | Dependent on engineering controls. In most circumstances – B<br>In situations of insufficient dust control – E or E (Dust Goggles instead of safety glasses) | |

| NFPA Standard 704 (2012) | Rating (Degree of Hazard) | Basis for Classification |
|---|---|---|
| Health | 1 | Inhalation Toxicity |
| Flammability | 0 | No known effects |
| Instability Hazards | 0 | No known effects |
| Special Hazards | None | |

## *HMIS III Standard*

By the criteria in this standard, FlexaTrac-NTA has the following classifications:

| HMIS III | Toxic Effect | Rating | Basis for Classification |
|---|---|---|---|
| Health | Skin Irritation | 0 | Non-irritating based on animal studies and human occupational exposure. Rating 1 is 0< Draize < 5 |
| | Eye Irritation | 1 | Serious Eye Irritation (GHS Rating 2), based on test of rabbits. Draize values not available, but effects seen in redness, discharge and corneal dullness. Rating 1 is 0< Draize <25. FlexaTrac-NTA would be within this range. |
| | Oral Toxicity | 1 | Oral toxicity to rats $LD_{50}$ = 1300-1600 mg/kg bw. Rating 1 is 500< $LD_{50}$ <5000 mg/kg |
| | Dermal Toxicity | 0 | Dermal toxicity to rabbits $LD_{50}$ >10,000 mg/kg bw. Rating 0 is $LD_{50}$ > 2000 mg/kg |
| | Inhalation Toxicity | 0 | Inhalation toxicity to rats $LC_{50}$ >5 mg/L. Rating 1 is 2.0< $LC_{50}$ ≥20 mg/L; Zero is chosen because the available number is a No Effect concentration; FlexaTrac-NTA is already rated a 1 for other reasons. |
| | Long Term Health | * | Due to FlexaTrac-NTA's IARC carcinogen status (IARC 2B), the Chronic Effect Indicator (*) is required under HMIS III |
| | Respiratory irritation | Not Rated | This endpoint is not addressed in the standard. FlexaTrac-NTA may be irritating to the respiratory tract. |
| Flammability | | 0 | FlexaTrac-NTA will not burn. FlexaTrac-NTA is not a dust explosion risk. While in some tests FlexaTrac-NTA dust was made to ignite, this was at an extreme and unsustainable concentration (2.25 kg/m3) and at very high spark energies. |
| Physical Hazard | | 0 | No known effects. FlexaTrac-NTA is a stable compound, and will not react with water. It is not an organic peroxide, explosive, compressed gas, a pyrophoric material or an oxidizer. FlexaTrac-NTA does not self-polymerize or self-react. |
| Personal Protection | Dependent on engineering controls. In most circumstances – B – Safety glasses, gloves should be sufficient. In situations of insufficient dust control – E or E (Dust Goggles instead of safety glasses) should be considered. PPE decisions should be made by appropriately trained and experienced safety professionals, should be suitable for the task being performed, and should be made in consideration of other hazards which exist in the area. | | |

## *NFPA Standard 704*

By the criteria in this standard, FlexaTrac-NTA has the following classifications:

| NFPA 704 | Toxic Effect | Rating | Basis for Classification |
|---|---|---|---|
| Health | Skin Irritation | 0 | Slightly Irritating based on animal studies and human occupational exposure. Rating 1 is "Materials that cause slight to moderate irritation to the…skin" |
| | Eye Irritation | 1 | Serious Eye Irritation (GHS Rating 2). Draize values not available, but effects seen in redness, discharge and corneal dullness<br>Rating 1 is "Materials that cause slight to moderate irritation to the … eyes..." |
| | Oral Toxicity | 1 | Oral toxicity to rats $LD_{50}$ = 1300-1600 mg/kg bw.<br>Rating 0 is 1000 < $LD_{50}$ < 2000 mg/kg |
| | Dermal Toxicity | 0 | Dermal toxicity to rabbits $LD_{50}$ > 10,000 mg/kg bw;<br>Rating 0 is $LD_{50}$ > 2000 mg/kg. |
| | Inhalation Toxicity | 0 | Inhalation toxicity to rats $LC_{50}$ > 5 mg/L.<br>Rating 2 is 2.0< $LC_{50}$ ≥10 mg/l. Zero is chosen because the available number is a No Effect concentration; FlexaTrac-NTA is already rated a 1 for other reasons. |
| | Respiratory irritation | 1 | FlexaTrac-NTA may be irritating to the respiratory tract. Rating 1 is "Materials that cause slight to moderate irritation to the respiratory tract..." |
| Flammability | | 0 | FlexaTrac-NTA will not burn. FlexaTrac-NTA is not a dust explosion risk. While in some tests FlexaTrac-NTA dust was made to ignite, this was at an extreme and unsustainable concentration (2.25 kg/m3) and at very high spark energies. |
| Instability | | 0 | No known effects. FlexaTrac-NTA is a stable compound and should not exhibit an exotherm under fire conditions |
| Special Hazards | FlexaTrac-NTA is not classified for any NFPA Special Hazard. It is not an oxidizer, does not react with water and is not a simple asphyxiant. | | |

# *References*


[1] World Health Organization. Nitrilotriacetic acid in Drinking-water - Background document for development of WHO *Guidelines for Drinking-water Quality,* 2nd ed. [Online] **1996,** *2*. http://www.who.int/water_sanitation_health/dwq/chemicals/en/nitrilotriaceticacid.pdf (accessed Jan 4, 2012).

[2] Proposition 65 Safe Harbor Levels: No Significant Risk Levels for Carcinogens and Maximum Allowable Dose Levels for Chemicals Causing Reproductive Toxicity [Online]; California Environmental Protection Agency, Office of Environmental Health Hazard Assessment, Reproductive and Cancer Hazard Assessment Branch: Sacramento, CA, November 2010. http://oehha.ca.gov/prop65/pdf/2010NovemberStatus.pdf (accessed Jan 4, 2012).

[3] *Expedited Cancer Potency Values and Proposed Regulatory Levels for Certain Proposition 65 Carcinogens* [Online]; California Environmental Protection Agency, Office of Environmental Health Hazard Assessment, Reproductive and Cancer Hazard Assessment Branch: Sacramento, CA, April 1992. http://www.oehha.ca.gov/prop65/pdf/expcancer.pdf (accessed Jan 4, 2012).

[4] Brouwer, N. M.; Terpstra, P. M. J. Ecological and Toxicological Properties of NTA as a Detergent Builder. *Tenside, Surfactants, Deterg.* **1995,** *32,* 225-228.

[5] *Risk Assessment Trisodium Nitrilotriacetate* [Online]; Human Health Section of the Comprehensive Risk Assessment Report Trisodium Nitrilotriacetate (NTA), Bundesanstalt für Arbeitsschutz und Arbeitsmedizin (BAuA): Dortmund, Germany, 2008. http://echa.europa.eu/documents/10162/17228/trd_rar_germany_nta_en.pdf (accessed Jan 4, 2012).

[6] European Commission Directive 2009/2/EC [Online], *Official Journal of the European Union, L 11* **2009,** *52*, 6-82. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:011:0006:0082:EN:PDF (accessed Jan 4, 2012).

[7] European Commission Regulation (EC) No 790/2009 [Online], *Official Journal of the European Union, L 235* **2009,** *52*, 1-439. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:235:0001:0439:EN:PDF (accessed Jan 4, 2012).

[8] *Screening Assessment for the Challenge: Glycine, N,N-bis(carboxymethyl)-(Nitrilotriacetic acid), 2010* [Online]*;* CEPA 1999; Environment Canada, Health Canada. http://www.ec.gc.ca/ese-ees/default.asp?lang=En&n=5D0D98DF-1 (accessed Jan 4, 2012).

[9] Nixon, G. A.; Butler, E. V.; Niewenhuis, R. J. Two-year feeding study with trisodium nitrilotriacetate and its calcium chelate. *Toxicol. Appl. Pharmacol.* **1972,** *21,* 244.

[10] NCI. *Bioassay of Nitrilotriacetic Acid and Nitrilotriacetic Acid, Trisodium Salt, Monohydrate for Possible Carcinogenicity.* DHEW 77-806; PB-266 177; NCI-CG-TR-6; Carcinogen Bioassay and Program Resources Branch, Carcinogenesis Program, Division of Cancer Cause and Prevention, NCI, NIH, Bethesda, MD, 1977. http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr006.pdf (accessed Jan 4, 2012).

[11] US EPA. EPA's Action Concerning Nitrilotriacetic Acid: Hearings Before the Subcommittee on Oversight and Investigations of the House Committee on Interstate & Foreign Commerce, 96th Congress, 2nd Session 301; Washington, DC, 1980.

[12] Cross, F. B. Beyond Benzene: establishing principles for a significance threshold on regulatable risks of cancer. *Emory Law Journal* **1986,** *35,*1-57.

[13] Goyer, R. A.; Falk, H. L.; Hogan, M.; Feldman, D. D.; Richter,W. Renal tumors in rats given trisodium nitrilotriacetic acid in drinking water for 2 years. *JNCI* **1981,** *66* (5), 869-874.

[14] Anderson, R. L.; Bishop, W. E.; Campbell, R. L. A Review Of The Environmental And Mammalian Toxicology Of Nitrilotriacetic Acid. *Crit. Rev. Toxicol.* **1985,** *15* (1), 1-102.

[15] IARC. Nitrilotriacetic Acid and Its Salts. *IARC Monogr. Eval. Carcinog. Risks Hum.* **1990,** Monograph 48, 181-212.
http://monographs.iarc.fr/ENG/Monographs/vol48/mono48-17.pdf (accessed Jan 4, 2012).

[16] IARC. Agents Classified by the IARC Monographs. *IARC Monogr. Eval. Carcinog. Risks Hum.* **2011**, *vol. 1–100*. http://monographs.iarc.fr/ENG/Classification/ClassificationsGroupOrder.pdf (accessed Jan 4, 2012).

[17] Capen, Dr. Charles. Director of IARC Expert Panel for Monograph 73. Private communication to Solutia Inc, 1999.

[18] IARC. Nitrilotriacetic Acid and Its Salts. *IARC Monogr. Eval. Carcinog. Risks Hum.* **1999,** Monograph 73, 385-399. http://monographs.iarc.fr/ENG/Monographs/vol73/mono73-19.pdf (accessed Jan 4, 2012).

[19] United Nations Economic Commission for Europe. *Substitutes for Tripolyphosphate in Detergents;* United Nations, 1992; Vol 73.

[20] Lewis, R. L. Monsanto Co. and Solutia Inc. Worker Mortality Studies- Chocolate Bayou, 1999.

[21] Anderson, R. L. The role of zinc in nitrilotriacetate (NTA)-associated renal tubular cell toxicity. *Food Cosmet. Toxicol.* **1981,** *19,* 639-650.

[22] *Bioassay of Trisodium Ethylenediaminetetraacetate Trihydrate (EDTA) For Possible Carcinogenicity.* DHEW 77-811; NCI-CG-TR-11; Carcinogen Bioassay and Program Resources Branch, Carcinogenesis Program, Division of Cancer Cause and Prevention, National Cancer Institute, National Institute of Health, Bethesda, MD, 1977. http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr011.pdf (accessed Jan 4, 2012).

[23] Secondary Direct Food Additives Permitted In Food For Human Consumption. *Code of Federal Regulations* [Online], Section 173.310, Title 21, 2009.
http://edocket.access.gpo.gov/cfr_2009/aprqtr/pdf/21cfr173.310.pdf (accessed Jan 4, 2012).

[24] *Household Cleansing Products;* Regulation Chapter X, Part 659; New York Department of Environmental Conservation: Albany, NY, 1985. http://www.dec.ny.gov/regs/4617.html (accessed Jan 4, 2012).

[25] *Review of Toxicity and Potential Biological Effects of NTA 2nd Report;* Environmental Health Directorate; Canada Department of National Health & Welfare: Canada, 1972; 283.

[26] Prakash, A. *NTA (Nitrilotriacetic Acid): An Ecological Appraisal;* Economic and Technical Review Report EPS 3-WP-76-8; National Research Council of Canada Associate Committee on Scientific Criteria for Environmental Quality, Marine Programs Division, Water Pollution Control Directorate, Environment Canada: Ottawa, Ontario, Canada, 1976.

[27] *Ecologo Standard CCD-105 Laundry Detergents and Fabric Softeners.* Environment Canada: Ottawa, Ontario, Canada, 1997. http://www.ecologo.org/en/seeourcriteria/details.asp?ccd_id=330 (accessed Oct 29, 2010).

[28] *Ecologo Standard CCD-061 Commercial Car Wash Service,* Environment Canada: Ottawa, Ontario, Canada, 1996.
http://www.ecologo.org/common/assets/criterias/ccd-061.pdf (accessed Oct 29, 2010).

[29] Federal Office of Public Health. Dispositions of the Federal Office of Public Health on the Classification of Substances Gift List 1 (List of Toxic Substances). *Federal Gazette.* (Engl. Transl.) Switzerland. **17 May 2005**, No. 19, p. 3065.

[30] Verordnung zur Reduktion von Risiken beim Umgang mit bestimmten besonders gefährlichen Stoffen, Zubereitungen und Gegenständen. *Chemikalien-Risikoreduktions-Verordnung (ChemRRV),* **18 May 2005,** Amended through 1 August 2011, SR 814.81, AS 2005 2917. http://www.admin.ch/ch/d/sr/8/814.81.de.pdf (accessed Jan 4, 2012).

[31] Assessment of the Practical Risk to Human Health from the Use of Nitrilotriacetic Acid in Household Laundry Products; Private report to the Proctor and Gamble Company; UAREP: Bethesda, MD, January 1985.

[32] *Ecological and Toxicological Properties of NTA as Detergent Builder;* Private report to the European Aminocarboxylates Committee; jointly owned by Ascend Performance Materials; Agricultural University Wageningen: UK, 1994.

[33] Assessment of Human Exposure to Sodium Nitrilotriacetate Monohydrate From the Use of Various Industrial/Institutional and Consumer Products; Private report to Monsanto Company. Available upon request from Ascend Performance Materials; Cantox Inc., February 1996.

[34] Anderson, R. L,; Alden, C. L.;, Merski, J. A. The Effects of Nitrilotriacetate on Cation Disposition and Urinary Tract Toxicity. *Food Chem. Toxicol.* **1982,** *20,* 105-122.

[35] Anderson, R. L.; Kanerva, R. L. Effect of Nitrilotriacetate (NTA) on Cation Balance in the Rat. *Food Cosmet. Toxicol.* **1978,** *16,* 563-568.

[36] BASF AG. *$^{14}$C-Trisodium Nitrilotriacetate in Trilon A liquid - Study of penetration through human skin in vitro;* Study jointly owned by Ascend as part of the European Aminocarboxylates Committee, January 2008.

[37] Ascend Performance Materials. *REACH Dossier for CAS 5064-31-3;* On file with the European Chemicals Agency: Finland, 2010.

[38] *NTA Powder;* Extended Safety Data Sheet (e-SDS) No. 1271 [Online]; Ascend Performance Materials: Cantonment, FL, Jun 22, 2011. Available upon request at stewardship@ascendmaterials.com

[39] Wendt, R. H.; Payne, A. G.; Hopping, W. D. Nitrilotriacetic Acid (NTA) Environmental Monitoring Program in Indiana: 1979 to 1983. *Environ. Toxicol. Chem.* **1988,** *7,* 275-290.

[40] McNeely, R. N.; Neimanis, V. P.; Dwyer, L. *Water Quality Sourcebook: A Guide to Water Quality Parameters;* Inland Waters Directorate, Water Quality Branch, Environment Canada: Ottawa, Ontario, Canada, 1979.

[41] Malaiyandi, M.; Williams, D.; O'Grady, R. A National Survey of Nitrilotriacetic Acid in Canadian Drinking Water. *Environ. Sci. Technol.* **1979,** *13,* 59-62.

[42] Matheson, D. H. *Nitrilotriacetic Acid (NTA) in the Canadian Environment,* Scientific Series No. 74; Inland Waters Directorate, Water Quality Branch, Environment Canada: Ottawa, Ontario, Canada, 1977.

[43] *Ecological Effects of Non-Phosphate Detergent Builders: Final Report on NTA.* Report to the Great Lakes Research Advisory Board of the IJC; International Joint Commission: 1978.

[44] California Regulatory Notice Register, 1992, 1234-1244.

[45] Phosphat-Ersatzstoffe bedrohen Wasserqualität. *Neue Zürcher Zeitung, Fernausgabe Nr. 216,* September 17, 1993, 41.

[46] Warren, C. B. Biodegradation of NTA and NTA Metal Ion Complexes: the Chemobiological Life Cycle of a Detergent Builder. In *Survival in Toxic Environments;* Khan, M.A.Q., Bederka, J., Eds,; Academic Press: New York, 1974; 473; as cited in Anderson et al, 1985.

[47] Walker, A. P. Ultimate biodegradation of nitrilotriacetate in the presence of heavy metals. *Prog. Water Technol.* **1975,** *7* (3/4), 555-560. As cited in Anderson et al, 1985.

[48] Shannon, E. E.; Schmidtke, N. W.; Monaghan, B. A. *Activated sludge degradation of nitrilotriacetic acid (NTA) metal complexes.* Water Pollution Control Directive Technology Development Report EPS 4-WP-78-5; Environment Canada Environmental Protection Services: Ottawa, Ontario, Canada, 1978.

[49] Björndal, H.; Bouveng, H. O.; Solyom, P.; Werner, J. NTA in sewage treatment, Part 3, Biochemical stability of some metal chelates. *Vatten,* **1972,** *28* (1), 5. As cited in Anderson et al, 1985.

[50] Tiedje, J. M.; Mason, B. B. Biodegradation of nitrilotriacetic acid (NTA) in soils. *Soil Sci. Soc. Am. Proc.,* **1974,** *38* (2), 278. As cited in Anderson et al, 1985.

[51] Backes, T. W.; Dingman, S. D.; Verrett, S. P. Block detergent containing nitrilotriacetic acid. U.S. Patent 5,490.949, February 13, 1996.

[52] Shimp, R. J.; Lapsins, E. V.; Ventullo, R. M. Chemical Fate and Transport in a Domestic Septic Tank System: Biodegradation of Linear Alkylbenzene Sulfonate (LAS) and Nitrilotriacetic acid (NTA). *Environ. Toxicol. Chem.* **1994,** *13* (2), 205-211.

[53] Guides for the Use of Environmental Marketing Claims. *Code of Federal Regulations,* Part 260, Title 16, 2008.

[54] Bernhardt et al. *Results of the Special Research Projects on Aspects of the Aquatic Environmental Compatibility of NTA;* Working Group 'NTA Monitoring and Special Research Program': Germany, 1991; 21-25.

[55] Hamm, A. Gewässerökologische Prüfung von NTA; Wirkung auf das Algenwachstum in komplexen Ökosystemen einschließlich der Einflüsse auf andere Glieder der aquatischen Biozönose; Aquatische Umweltverträglichkeit von NTA, Abschluß-Kolloquium der vom BMFT und BMU geförderten Sondervorhaben; KFA Karlsruhe: Deutschland, 1991; 130-192.

[56] Kucklentz. Influence of NTA, EDTA, Phosphate, and Copper on the Ecosystem of Ponds. Part 2: Zooplankton. *Verh. Internat. Verein Limnol.* **1991,** *24,* 2145-2148.

[57] Arthur, J. W.; Lemke, A. E.; Mattson, V. R.; Halligan, B. J. Toxicity of sodium Nitrilotriacetate (NTA) to the Fathead Minnow and an Amphipod in Soft Water. *Water Res.* **1974,** *8,* 187-193.

[58] Canton, J. H.; Slooff, W. Substitutes for Phosphate containing washing products: their toxicity and biodegradability in the aquatic environment. *Chemosphere* **1982,** *11* (9), 891-907.

[59] Toxicity Tests on the Fish, Lepomis macrochirus; the Snail, Physa heterostropha; and the diatom Navicula seminulum var. hustedtii for the Procter and Gamble Company; Academy of Natural Sciences Philadelphia: Philadelphia, PA, September 1967.

[60] Macek, K. J.; Strum, R. N. Survival and Gill Condition of Bluegill (Lepomis macrochirus) and Fathead Minnows (Pimephales promelas) Exposed to Sodium Nitrilotriacetate (NTA) for 28 Days. *J. Fish. Res. Board Can.* **1973,** *30* (2), 323-325.

[61] Bundesanstalt für Arbeitsschutz und Arbeitsmedizin (BAuA) Germany. *European Union Risk Assessment Report - TRISODIUM NITRILOTRIACETATE;* European Chemicals Bureau: Italy, 2007; Section 3.2.1.4.

[62] Bundesanstalt für Arbeitsschutz und Arbeitsmedizin (BAuA) Germany. *European Union Risk Assessment Report: edetic acid (EDTA);* European Chemicals Bureau: Italy, 2004.

[63] Swisher, R. D.; Crutchfield, M. M.; Caldwell, D. W. Biodegradation of Nitrilotriacetate in Activated Sludge. *Environ. Sci. Technol.* **1967,** *1,* 820-827.

[64] Rudd, J. W. M.; Hamilton, R. D. Biodegradation of Trisodium Nitrilotriacetate in a Model Aerated Sewage Lagoon. *J. Fish. Res. Board Can.* **1972,** *29* (8), 1203-1208, 10.1139/f72-176.

[65] Alder, A. C.; Siegrist, H.; Gujer, W.; Giger, W. Behaviour of NTA and EDTA in Biological Wastewater Treatment. *Water Res.* **1990,** *24* (6), 733-742.

[66] Klein, S. A. NTA Removal in Septic Tank and Oxidation Pond Systems, *Journal (Water Pollution Control Federation)* **1974,** *46* (1), 78-88.

[67] Moore, L.; Barth, E. F. Degradation of NTA Acid during Anaerobic Digestion. *Journal (Water Pollution Control Federation)* **1976,** *48* (10), 2406-2409.

[68] Shannon, E. E.; Fowlie, P. J. A.; Rush, R. J. *A study of nitrilotriacetic acid (NTA) degradation in a receiving stream;* Wastewater Technology Centre Technology Development Report EPS 4-WP-74-7; Environment Canada Environmental Protection Services: Ottawa, Ontario, Canada, 1974.

[69] *Waste Water Ordinance – AbwV (Ordinance on Requirements for the Discharge of Waste Water into Waters);* Federal Law Gazette, BGBl I; Federal Ministry for the Environment, Nature Conservation and Nuclear Safety: Germany, 2004; 1106.

[70] Wallace, A., Mueller, R. T., and Alexander, G. V., Effects of high levels of NTA on metal uptake by plants grown in soil, Agron. J., 66, 707, 1974.

[71] Cooper, E. M., Sims, J. T., Cunningham, S. D., Huang, J. W., Berti, W. R. Chelate-Assisted Phytoextraction of Lead from Contaminated Soils, *Journal of Environmental Quality* 1999. 28:1709–1719.

[72] Irtelli B, Navari-Izzo F. Influence of sodium nitrilotriacetate (NTA) and citric acid on phenolic and organic acids in Brassica juncea grown in excess of cadmium. *Chemosphere*. 2006 Nov;65(8):1348-54. Epub 2006 Jun 2.

[73] Borowiec, M., Huculak,M., Hoffmann, K., Hoffmann, J. Biodegradation of selected substances used in liquid fertilizers as an element of Life Cycle Assessment, *Polish Journal of Chemical Technology*, 2009, 11, 1-3

[74] Verhaar, H. J. M. *Trisodium Nitrilotriacetic Acid – Partitioning Behavior;* Private report to Ascend Performance Materials in support of REACH registration; Environ Corporation: 2010.

[75] The GHS fifth edition. The United Nations (2013). Publically available on the United Nations website: http://www.unece.org/fileadmin/DAM/trans/danger/publi/ghs/ghs_rev05/English/ST-SG-AC10-30-Rev5e.pdf (Accessed January 28, 2014)

[76] HMIS Chemical Ratings Guide, Appendix A. March, 2002. Available online at http://www.jjkeller.com/wcsstore/CVCatalogAssetStore/references/miscellaneous/hmis-downloads/9M-2.pdf (Accessed August 13, 2013)

[77] The NFPA Standard is available online for purchase at http://www.nfpa.org/codes-and-standards/document-information-pages?mode=code&code=704 (Accessed August 13, 2013)