ANALYSIS OF ALTERNATIVES

NON-CONFIDENTIAL REPORT

Legal name of applicant(s):	*DEZA, a.s.*
Submitted by:	*DEZA, a.s.*
Substance:	*Dibutyl phthalate*
Use title:	***Use in propellants*** *Sub-scenario 1: F-2: Industrial use as a burning rate surface moderant, plasticiser and/or coolant in the formulation of nitrocellulose-based propellant grains* *Sub-scenario 2: IW-2: Industrial use of propellant grains in manufacture of ammunition for military and civilian uses, and pyrocartridges for aircraft ejection seat safety systems [excludes propellants intended for manual reloading of ammunition cartridges by civilian users]*
Use number:	***2***

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A. USE OF DIBUTYL PHTHALATE IN PROPELLANTS

1 SUMMARY

1.1 Introduction

The applicant, DEZA, a.s. (hereafter referred to as "the applicant" or "DEZA"), is a Czech manufacturer of dibutyl phthalate (DBP), EC No. 201-557-4, CAS No. 84-74-2. DBP made by DEZA is consumed in a number of uses; one of the smaller ones is the use of the substance by a small number of EU-based companies in the formulation of propellant grains which are subsequently used in the manufacture of gun ammunition (typical small calibre ammunition for firearms) and, to a much lesser extent, as components of pilot ejection system on board military and civilian aircraft.

The scientific analysis presented in this document was performed by an independent third party (Risk & Policy Analysts Ltd), under contract to the applicant. The third party, acting as a trustee, has also handled, processed and synthesised the confidential business information received from individual downstream users (DUs) without sharing such information with the applicant or other third parties having due regard to the DUs' wishes for confidentiality.

1.2 Role of DBP in propellants and final products of concern

This AoA covers Use No 2 of DBP, Use in propellants, which, as described in the Chemical Safety Report (CSR), encompasses two sub-scenarios:

- **Formulation 2: Industrial use as a burning rate surface moderant, plasticiser and/or coolant in the formulation of nitrocellulose-based propellant grains**[1]
- **Industrial Use 2: Industrial use of propellant grains in manufacture of ammunition for military and civilian uses, and pyrocartridges for aircraft ejection seat safety systems [excludes propellants intended for manual reloading of ammunition cartridges by civilian users]**

These two sub-scenarios are considered together for the purposes of this AoA, for the following reasons:

- from the perspective of the applicant, the alternatives discussed here apply equally to both;
- the processes described by the two sub-Scenarios are undertaken by actors downstream of the applicant, in the same supply chain (on occasion both are undertaken by the same downstream user); and
- it avoids repetition of the discussion and analysis.

The use of DBP in propellants is characterised as follows:

- **Tonnage and concentration in propellant mixtures**: the use of DBP in the formulation of propellants is one of the smaller uses for the substance in terms of tonnage, as shown in the

[1] The term 'grains' can interchangeably be used with the term powder or formulation.

CSR. Additionally, the concentration of DBP in the nitrocellulose-based propellant mixtures is relatively low, typically 2-5% (see Section 2.2.4.2); and

- **Role of DBP in propellants**: DBP is generally known as a phthalate ester plasticiser in PVC. However, its role in propellant is generally much more niche. DBP may primarily act as a:

  (a) surface moderant (also known as 'deterrent') for the propellant powder grains, i.e. it reduces their burning rate, thus controlling the velocity and ballistic performance of the projectile (bullet). Well over 90% of the amount of DBP used in propellants is used specifically with the aim of demonstrating this moderating role; or

  (b) plasticiser to facilitate the processing properties of propellants. This plasticising role is minor compared to the one above and has been found to be relevant to <<10% of the tonnage of DBP used in propellants.

Information from consultation and a literature review has identified the following final products that may contain DBP-containing propellants (see Section 2.2.3):

- small calibre firearm ammunition (assumed in this AoA to refer to calibres of ≤20 mm) primarily for military use and to a much lesser extent civilian (sport shooting/hunting) use;
- medium and large calibre military ammunition (>20 mm), including large calibre naval and land gun ammunition and propellant charges for large calibre guns; and
- pyrocartridges, i.e. components of armed ejection seats found on board military and civilian aircraft.

Among these products, two are the most critical ones:

- small calibre ammunition that is used in the standard rifles and handguns of national armies on NATO member nations – without this ammunition armies across the EU would face severe operation capability issues; and
- pyrocartridges for ejection seats – these components of ejection seat mechanisms are present in training aircraft of several national military air forces both in the EU and outside the EU, but also in a number of civilian aircraft that are used by aerobatics teams and a growing number of private users. The reliable functioning of aircraft ejection seats can literally prove to be a matter of life and death in the case of an accident or other emergency.

Important Note: Uses not supported in this Application for Authorisation

Until now, a very small proportion of DBP-based propellant powders have been intended for use by licensed individual sport shooters and hunters for the manual, private reloading of empty cartridges. **This use of DBP-based propellants is not supported by the applicant and it is not within the scope of this Application for Authorisation**.

More generally, this **Application does not cover any direct consumer use of the substance or its mixtures, which may feasibly and foreseeably result in consumer exposure to the substance**.

DBP-based mixtures are hermetically sealed inside small calibre ammunition cartridges which may be used by sportsmen/women, hunters and shooting enthusiasts. When present inside ammunition rounds, DBP is not accessible to the user and the user will not be exposed to DBP under any foreseeable conditions of normal and safe use.

1.3 Identification and screening of potential alternatives

There are several theoretical options for the elimination of DBP from propellant mixtures, as identified through a combination of literature review and consultation with DUs (see Section 3.2):

- substitution of DBP in the mixtures by non-energetic alternative substances (43 potential alternative substances have been identified);
- substitution of DBP in the mixtures by energetic alternative substances (34 potential alternative substances have been identified);
- replacement of DBP-based mixtures by alternative propellant mixtures that are based on technologies that do not rely on DBP (six alternative technologies have been identified, including extrusion of propellants, rolling of propellants, manufacture of propellants by extrusion-impregnation, Low Vulnerability Ammunition (LOVA), extruded composite low vulnerability technology and liquid gun propellants).

This AoA explains (see Section 3.1.1) that the applicant is a chemicals manufacturer with specialisation in the manufacture of esters, for instance, phthalate esters. The applicant can under no circumstances manufacture energetic substances neither can they supply alternative technologies to their downstream users; therefore, **the only alternatives that can be of relevance to the applicant and to this AoA, which has been undertaken from the perspective of the applicant, are potential alternative non-energetic substances**. The other options are considered in the SEA (in its Annex 7, which explains why these technologies are not technically and economically feasible or indeed available for the affected DUs).

With this established scope of the analysis, the screening of the initial list of forty-three potential alternative substances was undertaken (see the discussion of the screening process in Section 3.3.2 and the Confidential Annex) and this has resulted in the following shortlist of ten potential alternative substances, which have been assessed in detail in this AoA.

Table 1.1: Alternative substances assessed in detail in the Analysis of Alternatives

Potential alternative	EC number	CAS number
Methyl centralite (1,3-dimethyl-1,3-diphenyl urea)	210-283-4	611-92-7
Ethyl centralite (1,3-diethyl-1,3-diphenyl urea)	201-645-2	85-98-3
Akardite I (1,3-diphenyl urea)	203-003-7	102-07-8
Akardite II (3-methyl - 1,1-diphenyl urea)	236-039-7	13114-72-2
Akardite III (3-ethyl-1,1-diphenyl urea)	242-052-9	18168-01-9
Bis(2-ethylhexyl) adipate (DEHA)	203-090-1	103-23-1
Acetyl tributyl citrate (ATBC)	201-067-0	77-90-7
Tributyl citrate (TBC)	201-071-2	77-94-1
Dioctyl azelate (DOZ)	203-091-7	103-24-2
Isodecyl pelargonate (IDP)	203-665-7	109-32-0

1.4 Assessment of suitability and availability of potential alternative substances

1.4.1 Findings on the technical suitability of potential alternative substances

Two parallel analyses have been undertaken in this AoA:

- as required by the REACH Regulation, the 'main' assessment of the technical feasibility of the selected potential alternative substances has been undertaken from the perspective of the applicant. This has focused on the capabilities of the applicant to produce now and in the future each of the shortlisted alternative substances in terms of manufacturing knowledge and expertise, access to and handling issues for precursors to the alternatives and the foreseeable level of demand for the alternatives by DUs; and
- the perspective of DUs has also been considered. More specifically, the technical feasibility of the selected potential alternative substances for the DUs has also been taken into consideration because only alternatives that would (in principle) be technically feasible would make realistic alternatives for the applicant to (start to) manufacture and place on the market. Eight comparison criteria have been identified as relevant to the assessment of the technical feasibility of potential alternative substances from the perspective of propellant manufacturers and their customers: (a) plasticising effect, (b) solubility in water, (c) reduction of burning velocity of the propellant, (d) diffusion rate, (e) melting point and boiling points, (f) heat of explosion, (g) migration during storage and ballistic shelf-life, and (h) chemical shelf-life (see Section 2.3.1.2 and the Confidential Annex).

From the perspective of the applicant, only one out of the ten shortlisted potential alternative substances can be considered technically feasible, DEHA. DEHA is already manufactured by the applicant, therefore access to its precursors and manufacturing technology is already in place. However, DEHA is only suitable as a plasticiser and as such could only be feasibly used as a substitute for DBP in a small minority of cases (<<10% of the tonnage of DBP currently used).

No other potential alternative substance can be readily manufactured by the applicant. The Confidential Annex to this AoA (Section 4.1.1) explains that:

- all urea derivatives (centralites and Akardites) require precursors that either have a poor hazard profile or are made with technology which is unavailable to the applicant and incompatible to their esterification plant;
- for other potential alternative substances, the applicant has either poor knowledge of precursor availability or has established knowledge of market shortages of the required precursors; and
- for the remaining potential alternative substances for which precursors could be obtained in the open market, the applicant does not have access to the required manufacturing technology, which could allow their production at the industrial scale.

From the perspective of the DUs, the following define the technical feasibility of the selected potential alternative substances:

- not all potential alternative substances may be both technically feasible moderants and technically feasible plasticisers. Centralites and Akardites are only (theoretically) suitable as alternative moderants, while DEHA, DOZ and IDP may only be used as alternative plasticisers. Only citrates (ATBC and TBC) appear to display promising technical characteristics for use both as moderants and plasticisers. However, citrates would be accompanied by changes to the production process of propellant manufacturers, such as temperature increases which in term

may affect the stability of the propellant powder, and longer impregnation times making them unsuitable for certain ammunition calibres;

- urea derivatives, particularly centralites, are used as stabilisers in nitrocellulose-based propellant mixtures. In such matrices, they are often associated with the formation of carcinogenic decomposition products (see Section 4.2.2.2). As a result, on-going research has aimed at the replacement of these stabilisers in nitrocellulose-based propellants. From a technical, scientific and innovation point of view, use of centralites (and to a lesser extent Akardites) as moderants would not be considered a forward step in the field of propellant manufacture;
- importantly, for any potential alternative substance, technical feasibility will only be proven through extensive R&D. The alternatives have so far been subject to very limited research by propellant manufacturers as potential substitutes for DBP and mostly for their role as moderants, which is the most critical. The R&D programmes of propellant manufacturers are still at a too early a stage for robust conclusions of technical suitability to be reached (see Section 5.6.1 and the Confidential Annex);
- even if any alternative substance proves to be suitable in laboratory tests, pilot scale trials and industrial scale production runs, both the reformulated propellants and the ammunition and pyrocartridges that contain them need to undergo a re-qualification process to ensure that the new products meet existing military and civilian standards (see Section 2.3.2). The re-qualification process is not only lengthy (up to 60 months for a single NATO-qualified small calibre ammunition, see Confidential Annex, Section 5.6.1) but also considerably expensive not only for the propellant manufacturer but also for companies downstream (ammunition and aircraft manufacturers). Table 5.8 and Table 5.13 in the Confidential explain that re-qualification could cost several millions of Euros and would take several years to complete.

Overall, the only alternative substance that is currently technically feasible for the applicant is DEHA and this cannot meet the requirements of the DUs for the vast majority of DBP-based propellant mixtures.

1.4.2 Findings on the risk reduction potential of potential alternatives

The analysis of the selected non-energetic potential alternative substances has concluded the following:

- risks to the employees of the applicant's DUs (propellant and ammunition manufacturers) are currently adequately controlled below the effect threshold for DBP, as shown in the CSR that accompanies this AoA. Therefore, the substitution of DBP by any alternative substance would not confer any discernible benefit to these workers' health. No risk to the users of propellant or ammunition or to the environment is envisaged from the use of the ammunition that contains DBP-based propellants;
- when the hazard profiles of alternatives are compared to that of DBP, it appears that the alternatives generally have a more benign profile. For the endpoint for which DBP was listed on Annex XIV of the REACH Regulation (reproductive toxicity), none of the selected potential alternative substances, apart from DEHA (listed for Substance Evaluation because of concern regarding its reprotoxicity, in part relating to its structural similarity to DEHP), appears to raise any concern (see Table 5.2 and Table 5.3, and the Confidential Annex);
- concerns may exist for the selected alternatives with regard to acute toxicity (which has been generally found to be low), irritancy (inhalation, skin and eye are affected by the majority of the potential alternatives), repeat dose toxicity (ATBC) and aquatic toxicity (the majority of the

potential alternatives). Tentative concerns on the endocrine disruption potential of some (DOZ and IDP) have also been identified (see Table 5.2 and Table 5.3, and the Confidential Annex); and

- the majority of the selected alternatives have not been adequately researched and many of the preliminary conclusions reached in this AoA are based on the results of alternative testing approaches. Only for five substances, ethyl centralite, DEHA, ATBC, TBC and DOZ, registration dossiers have been found on ECHA's Dissemination Portal[2]. For some of the potential alternatives (Akardite I & III and IDP) the lack of information renders any comparison to DBP extremely uncertain.

Finally, from the perspective of the health and safety of workers of the applicant, the handling of precursors to the five urea derivatives (the two centralites and the three Akardites) could raise significant concerns, as explained in the Confidential Annex to this AoA.

1.4.3 Findings on the economic feasibility of potential alternatives

The selected potential alternative substances can be classified into three sub-groups according to their economic feasibility characteristics:

- **DEHA**: this is the only one of the potential alternatives that is currently manufactured by the applicant. Therefore, its manufacture is certainly economically feasible. However, DEHA would only be able to replace a very small percentage of current DBP sales in the field of propellants as it can only act as a substitute plasticiser. Selection of this substance as a substitute for DBP would result in economic loss for DEZA;

- **urea derivatives**: this sub-group includes the two centralites and the three Akardites. The applicant cannot manufacture these due to the technical limitations of their existing plant. Conversion to one of those would be very long and exceedingly costly when considering the lack of certainty on the technical feasibility for each of these substances for the DUs and also the very modest tonnage that the applicant would foreseeably be able to successfully sell to its customers; and

- **other alternative esters**: this sub-group includes the two citrates, IDP and DOZ. The Confidential Annex to this AoA (Table 4.8) explains that costly plant conversion may be needed, but not for all potential alternative substances within this sub-group. The development of expertise in their manufacture would take a considerable time and the amount that the applicant would potentially be able to sell would be too low to justify the associated expenditure in R&D and investment (particularly for DOZ and IDP which might only act as substitute plasticisers).

For the majority of the potential alternative substances, established suppliers appear to be presented in the EU market. Therefore, it would be reasonable to assume that the applicant might face difficulties in setting a foothold in the market as a new manufacturer of any of these potential alternative substances, especially given the low envisaged demand for these substances by their DUs.

[2] As of 28 February 2013, the ATBC entry appeared to have been removed from the Portal. Searches undertaken in June 2013 confirmed the absence of the substance's entry in the Portal.

Overall, as a result of a refused Authorisation, the applicant would forfeit the turnover associated with DBP sales to propellant manufacturers without being capable of replacing this with sufficient revenue from sale of alternative substances. Therefore, the identified potential alternatives cannot be considered economically feasible (details on turnover to be lost by the applicant are given in the SEA, Section 2.2.2.1).

Important Note: Economic impacts on downstream users – Summary of key SEA findings

The SEA goes beyond the economic impacts on the applicant and analyses the costs for DUs associated with the use of these alternatives and from a refused Authorisation for DBP more generally. The SEA explains that a refused Authorisation would:

- jeopardise the viability of downstream user production plants (SEA, Section 1.3.2.1);
- have severely detrimental effects on the capability of the EU ammunition manufacturing industry to manufacture the most critical small calibre ammunition used in the standard rifles of the national armies of EU Member States (SEA, Section 2.2.2.3)
- adversely affect the competitiveness of EU ammunition manufacturers as it would make it much easier for non-EU manufacturers of ammunition to replace them in the role of suppliers of ammunition to EU Ministries of Defence (SEA, Section 2.2.2.4);
- affect the market that supplies ammunition to civilian users particularly competition sport shooters, who rely on high-performance small calibre ammunition (SEA, Section 2.3.3.1); and
- impact upon the airworthiness of several aircraft operated by certain EU national military air forces and of civilian aircraft that are operated by professional aerobatics teams and private users, due to the inability to replace the ejection seat DBP-containing pyrocartridges at the interval specified by the aircraft manufacturer (SEA, Section 2.2.3.4).

1.4.4 Findings on the availability of potential alternatives

Of all alternatives, only one, DEHA, is available to the applicant. Phenyl ureas cannot become available without an entirely new production facility and alternative esters (other than DEHA) would require lengthy testing and development of the required knowledge and technology before production at the industrial scale becomes feasible. The current demand for DBP in the explosives sector is too low to make such a proposition financially viable and realistic.

1.5 Actions needed to improve the suitability and availability of potential alternatives

The applicant is not in a position to undertake extensive R&D for the development of a suitable substitute for DBP in propellants. The quantity of DBP currently sold to propellant manufacturers is too small to justify major investment in the investigation and introduction of new technology that would allow the manufacture of the alternatives. In any case, DEZA would only initiate work on the production of any alternative substance on the request of its DUs, if the latter had robust evidence of the alternative's technical feasibility for use in the formulation of propellants. Such a request has not been received so far.

On the other hand, DUs have been undertaking R&D work with the aim of developing a technically suitable alternative for DBP for their propellants for ammunition products. This planned work is envisaged to entail a considerable cost and is expected to deliver a result after several years (as described in the Confidential Annex to this AoA, Section 5.6.1).

As with any R&D programme, there is no guarantee that a suitable alternative substance that addresses the requirements of all propellant formulations will be found. Neither can it be assumed that the most suitable alternative will necessarily end up being one of the selected alternative substances examined in this AoA. Moreover, the R&D phase will have to be followed by a re-qualification procedure for each propellant type and each ammunition product (see description in

Section 2.3.2). This re-qualification process will be long and will be accompanied by a significant cost for both propellant and ammunition manufacturers, as shown in the Confidential Annex to this AoA (Section 5.6).

2 ANALYSIS OF SUBSTANCE FUNCTION

2.1 Introduction to propellants relevant to this Application for Authorisation

Propellants are low explosive materials that burn slowly in a controlled manner resulting in a large volume of hot gases. These gases are typically used to impart motion to and propel a projectile, such as a bullet, shell, rocket or missile (Agrawal, 2010). Thus, propellants are predominantly used in guns, rockets and munitions and are often categorised as such (Agrawal, 2010); however, generated gases from propellants can also be used to produce mechanical action such as drive pumps, empty tanks, actuate valves, inflate air bags, etc. (Mukhopadhyay & Datta, 2007). An overview of different propellant types is given in Figure 2.1 below. The part of the chart circled in red indicates the types of propellant in which DBP may be used in the supply chain of the applicant. It should be noted that DBP is only used in solid propellants where nitrocellulose acts as the binder. Therefore, alternative substances should be suitable for this particular type of propellants.

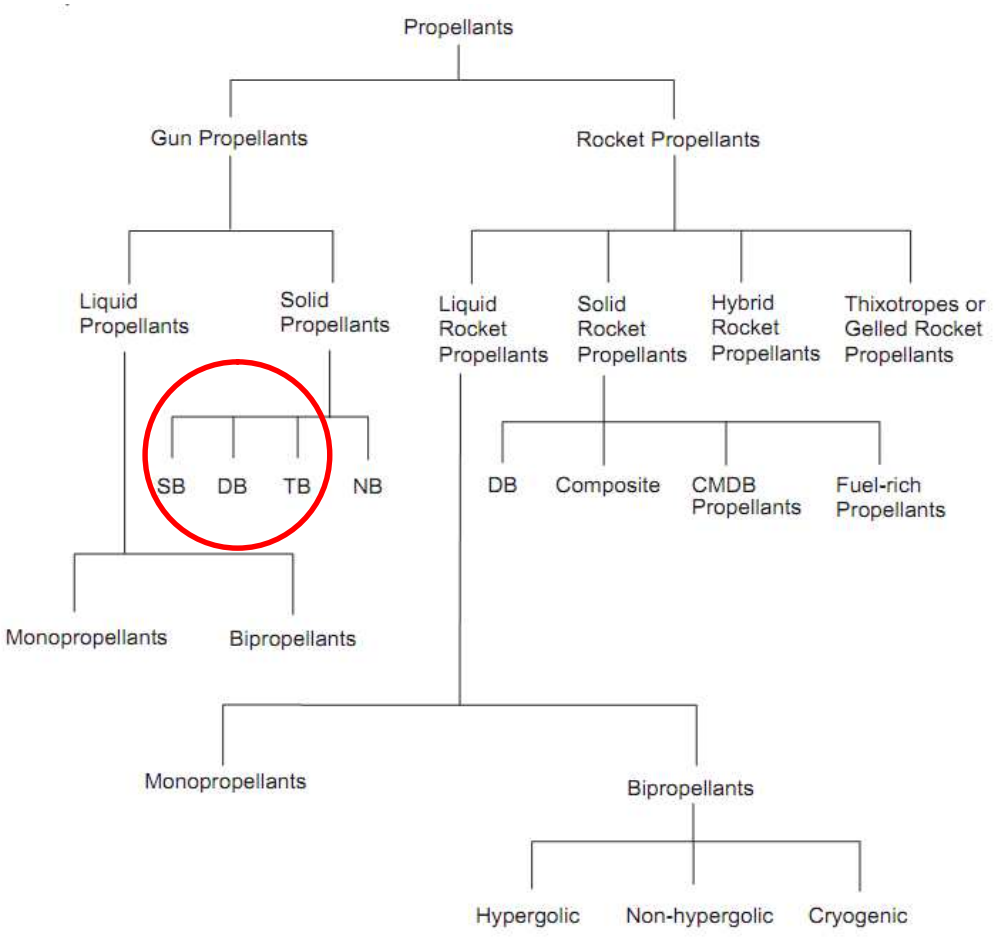

Figure 2.1: Overview of propellant types by application (Agrawal, 2010)

Note: SB = single-base, DB = double-base, TB = triple base, NB = nitramine-base

As shown in the Figure, propellants can be broadly classified into liquids or solids. Solid propellants are typically known as smokeless powders, although they are neither powders nor completely smokeless. The basic types among these include (Kirchner & al, undated):

- **single-base**, which are prepared by dissolving nitrocellulose in ether and alcohol;
- **double-base**, which are prepared by dissolving nitrocellulose in nitro-glycerine; and
- **triple-base**, which are prepared by dissolving nitrocellulose in nitro-glycerine with nitroguanidine added to reduce the temperature of the combustion-produced gas.

Whether the propellant should be single-, double- or triple-base and the exact composition of the propellant depends on the requirements of users, thus no single formulation meets all users' requirements.

Figure 2.1 suggests that DBP is used **in gun propellants**. These are nitrocellulose-based mixtures that are used in ammunition pieces for small, medium and large calibre guns. Gun propellants are manufactured in granular or other shape (known as grains) to give a constant burning surface without detonation and are used with the aim of propelling a solid projectile (e.g. a bullet) (Akhavan, 2011).

Another application of propellants that are of relevance to this AfA is in **cartridge-actuated devices** (CADs). CADs are small, self-contained energy sources that are used to do mechanical work. The energy is generated by the burning of a propellant or pyrotechnic material and is often used to push a piston or initiate an explosive train. This differentiates CADs from similar devices, such as rocket igniters, where heat energy, not mechanical work, is the desired output (Grote, undated). CADs find wide use in the aerospace and military sectors with examples including thrusters/removers, cable cutters, explosive bolts/nuts systems, safe/arm & arm/fire devices, gas generators, ignition elements, laser ordnance, inflation and fire extinguishing devices, escape system sequencers, and rocket catapults and thrusters (Valenta, 2009). By way of example, on a F-18 fighter jet, a significant number of CAD systems may be found in the aircrew survival equipment, the aircrew escape sequencing system, the engine/Auxiliary Power Unit fire extinguishing system and elsewhere (Blachowski, undated). In the case of DBP, specific propellant formulations that contain the substance are used in pyrocartridges which are located in the ejection seat mechanisms of military and civilian aircraft.

2.2 Use of DBP in the formulation of propellant grains and use of propellants in ammunition and aircraft pyrocartridges

2.2.1 Use of DBP in the manufacture of propellants

DBP is typically added single-base, double-base and triple-base propellant formulations (see basic components mentioned above) through proprietary manufacturing processes. The mixing of the different components of propellants can be performed either in a solvent or water phase. DBP may be present either on the surface of the propellant grain or inside the grain but the most critical applications are those where DBP acts on the surface as a surface moderant. Mixing of the DBP-based formulations is typically followed by ancillary processes such as washing and drying of the propellant and mechanical processes such as rolling, shaping, pressing and extrusion to create the different propellant grains. Details of the processes cannot be provided as DUs do not wish to share their details with neither the public nor the applicant; the know-how of manufacturing the propellants is a closely guarded company secret for each user of DBP.

Once the propellant formulation is complete, the fate of the propellant will vary:

- it may sold by the propellant manufacturer to an ammunition manufacturer who will use it to load ammunition cartridges and thus fabricate the final product (e.g. a rifle cartridge, shotgun shell or pistol cartridge) – this is by far the most common scenario;
- some propellant manufacturers may use their own DBP-based propellant to manufacture propellant charges in-house, which are then sold to final users, e.g. a national army – a propellant charge is a tube (a cartridge case), in which there is the propellant and an ignition system. Propellant charges are used exclusively in propelling large calibre projectiles; or
- some propellant manufacturers may use their DBP-based propellant to manufacture the complete final product in-house, which is then sold to the final user, e.g. a national army.

2.2.2 Functionalities of DBP

DBP plays three distinct roles in propellant mixtures. It may act as:

- a **moderant**: gun propellants need to have their mass burning rate reduced during the early part of the combustion process, to slow the rise of chamber pressure. Propellants can burn so rapidly that the initial rise of chamber pressure in a weapon may be faster than desired. The rate of burning depends on the gas pressure, since an increase in gas pressure causes an increase in the rate of burning on the surface of each grain and conversely, the rate of burning falls with reduced gas pressure. Control of the rate of burning and hence gas pressure is possible by varying the chemical composition of the propellant and by the choice of the geometrical shape of the grain and its surface area (the larger the surface area of the grain, the greater is the amount of gas evolved per unit of time). Any rapid rise in chamber pressure adversely affects the velocity of the projectile (the reader is also referred to the discussion on progressive, degressive and neutral propellants presented in Annex 7 of the SEA (Section 5.7.3)).

  Alteration of the composition of the propellant is performed by the addition of a moderant, and DBP can be one of these moderants. DBP may act as a moderant both when used for the surface treatment of propellant grains and when used as admixture for its incorporation inside the mass of the propellant;

- a **plasticiser**: in order to convert nitrocellulose in a propellant from its natural fibrous state into a gel, it must be treated with a solvent. This may either be a volatile one subsequently removed by evaporation (single-base propellants), or nitro-glycerine within double- and triple-base propellant compositions. In either case, the process may require the assistance of a plasticiser (Bailey & Murray, 2000). The plasticiser is used as an additive to increase the flexibility, softness and workability/processability of the propellant. This agent is responsible for the reduction in tensile strength and elastic modulus of the material. The addition of plasticiser to the propellant composition provides properties suitable for storage, application and transportation (Libardi, Ravagnani, Morais, & Cardoso, 2010).

There are two categories of plasticisers used in propellants (Agrawal, 2010):

- **non-energetic plasticisers** modify tensile strength, elongation, toughness and softening point but reduce the energy of the system; and
- **energetic plasticisers** enhance flexibility and elasticity in addition to increasing the overall energy of a system and its spontaneous ignition properties[3]; and

- a **coolant**: literature and consultation suggests that DBP also acts as a coolant for propellants. As a coolant, DBP adsorbs heat when a propellant is decomposed during combustion, thus imposing a limit on the flame temperature of propellants in order to minimise erosion of the bore and other undesirable effects (Bailey & Murray, 2000) (Akhavan, 2011). Consultation has confirmed that this is an all-around important role but particularly critical for some types of powders for which the heat of explosion is required to be lower (large calibre ammunition and combustible charges for large calibre munitions).

It is worth pointing out the following:

- the first two functionalities are the most critical, the cooling effect is of lesser importance when selecting an alternative but still important in terms of the advantages that DBP-based ammunition has over DBP-free alternatives. Propellant manufacturers would consider the cooling effect of a substitute to DBP during the preliminary thermodynamic studies of potential alternatives, but they would primarily have to focus on the two main roles of DBP, its deterrent and plasticising effects; and
- DBP is typically used to deliver only one of the two critical functionalities, i.e. in some propellants it is used specifically to act as a moderant of the burning rate while in other propellants, DBP is used to act as a plasticiser. Moreover, for different propellant manufacturers, the importance of one or the other function may vary: for some the moderating effect is more important while for others the plasticising effect is more important, depending on the products each one manufactures.

Consultation with the DUs confirms that the moderating effect is by far the most important: >>90% of the tonnage of propellants currently manufactured with DBP rely on the substance's effect of moderating the burning rate. Only a small minority of the all propellants manufactured rely on the ability of DBP to plasticise the propellant mixture and allowing it to be easily passed through an extruder.

Key point 1

For the "Applied for" Use, DBP is primarily used as a surface moderant and to a lesser extent as a plasticiser in propellant formulations

Not all alternative substances may be both technically feasible moderants and technically feasible plasticisers and some alternatives may or may not be suitable for replacing DBP in specific propellant products. It should be clear that any given propellant manufacturer may use DBP as a moderant in some of their propellant formulations and as a plasticiser in other propellant

[3] Energetic plasticisers may sometimes be preferred because of their contribution to energy (Agrawal, 2010); however, safety and cost considerations often demand that non-energetic plasticisers are used (KilnFired.com, undated). DBP is a non-reactive non-energetic plasticiser.

formulations. Therefore, their requirements for an alternative substance will not be uniform across their entire portfolio of propellant products.

Key point 2

Any given potential alternative substance may show different technical feasibility when used as a substitute surface moderant as opposed to its potential use as a substitute plasticiser in propellants

The juxtaposition of these two roles of DBP is shown in Table 2.1. The Table demonstrates which DBP-containing products would likely be threatened by a refused Authorisation and confirms that of particular importance is the use of DBP as a moderant in the formulation of propellants used primarily in small calibre ammunition for military use.

Table 2.1: Description of the importance of the two key functionalities of DBP in propellants

	Moderant	**Plasticiser**
Mode of use	Improves barrel pressure/bullet velocity ratio; typically (but not exclusively) used on the surface of the propellant	Plasticiser used in the mass of the propellant
Typical calibres	Small calibre ammunition	Medium/large calibre ammunition, very limited use in small calibre ammunition; aircraft pyrocartridges
Military vs. civilian use	Mostly military Military vs. civilian: ca.4:1	Almost exclusively military
Tonnage of DBP-based propellants	>>90% of all propellants based on DBP	<<10% of all propellants based on DBP
Number of relevant propellant types	In the range of 10-100; larger than plasticiser types	In the range of 10-100; smaller than moderant types
Production process	Mainly water phase (with some solvent-phase mixtures)	Mainly solvent phase (with some water-phase mixtures)
Form of propellant	Generally, spherical grains ("ball powder"); only some extruded shapes	Extruded shapes
Important final products depending on DBP (examples)	NATO-qualified small-calibre ammunition: 5.56 mm, 7.62 mm, 9 mm and 12.7 mm calibres, widely used in the standard rifles of the armies of both NATO member nations and non-NATO nations*. These types of ammunition are of paramount importance to the operational capabilities of armed forces and to national security	Naval ammunition Terrestrial army munitions Aircraft pyrocartridges used in the ejection seats of military and civilian aircraft
Further information provided in	AoA, Section 2.3.2 SEA, Section 1.1.3.2	SEA, Section 1.1.3.2

Source: Consultation
** NATO member nations include 22 EU Member States (BE, BG, CZ, DK, EE, FR, DE, EL, HR, HU, IT, LV, LT, LU, NL, PL, PT, RO, SK, SI, ES, UK) and 6 non-EU countries (Albania, Canada, Iceland, Turkey and the USA). Annex 3 of the SEA shows that NATO-qualified calibre ammunition is used in the standard issue rifles used by the military/security forces of the vast majority of EU Member States*

Key point 3

The theoretical substitution of DBP by an alternative substance in the "Applied for" Use cannot follow a 'one size fits all' approach. More specifically, in small calibre ammunition, DBP's role is most critically that of a surface moderant. Given the importance of small calibre ammunition for DBP-based propellants, surface moderation is the key functionality of DBP on which particular emphasis will be given in this AoA and the SEA

2.2.3 Products containing DBP in the EU

2.2.3.1 Description of products

The products manufactured by the supply chain covered by this AfA include (in order of decreasing importance in terms of tonnage of propellants manufactured):

- military/security forces small calibre ammunition;
- sport/hunting small calibre ammunition;
- medium and large calibre military ammunition; and
- aircraft pyrocartridges.

With regard to **ammunition**, the number of DBP-based types (formulations) and the number of individual propellant products (each propellant type may come in a number of products-variations), Table 2.2 summarises the available information.

Table 2.2: Types of final products containing DBP-based propellants within the supply chain

Product category	Single-, double-, or triple-base formulations	Number of DBP-based types	Number of individual propellant products
Small calibre ammunition	Double-base and single-base	10-100	100-1,000
Medium and large calibre ammunition	Mainly double-base and single-base but also some triple-base		
Source: Consultation (additional detail is given in Table 1.9 in the SEA)			

When considering the classification of calibres, the following should be noted:

- the separation of calibres to "small" (assumed to be ≤20 mm) and "medium" and "large" (assumed to be >20 mm) is indicative, as different countries, companies and experts may use different 'cut-off' values for these categories. It would also appear that the terms are used in variable ways in different contexts (for example, in naval ammunition a 40 mm round is considered 'small'); and
- some of the DBP-based propellants can realistically be used in several calibres. The propellant manufacturers do not always know with certainty in which calibres and for which weapon the customer will use each of the supplied propellant formulations.

It should also be noted that, in this AoA, the distinction of propellants between "civilian" and "military" is largely based on the propellant manufacturers' best knowledge – they may not always know for what purpose their propellants will be used, into which cartridges and for which type of weapon it will be loaded. Furthermore, whether police use of ammunition is considered to be a civilian or military use may differ amongst different countries. For example, in some countries, police use is a civilian use, however, the composition of and qualification required for these products is identical to ammunition used by the military. This AoA takes the approach of considering police force ammunition alongside military ammunition and in general, where any reference is made to military ammunition, this should be assumed to include police/security forces ammunition as well.

Beyond ammunition, DBP is present in **pyrotechnic components for aircraft rescue systems** in certain types of aircraft. The affected aircraft types are discussed in detail in the SEA (see Section 1.1.3.5); it can be disclosed that the aircraft have been very popular over several decades with almost thousands of units produced over several decades and more than 1,000 units still being flown by national armies and civilians around the globe (see SEA, Section 1.1.3.5). Aircraft pyrocartridges of the type relevant to DBP in the "Applied for" Use include a shell body in the form of a steel cartridge case; the propellant charge consists of single- or double-base powder, and the ignition is mechanical or electrical. The pyrocartridge containing the propellant with DBP is designed to activate the telescopic pull-out mechanism of the pilot's/co-pilot's rescue seat to allow them to eject away from the aircraft before the parachute is safely deployed in the case of an emergency. The number of propellant formulations used in aircraft pyrocartridges cannot be disclosed but can be confirmed to be far fewer than formulations for use in ammunition.

Key point 4

DBP plays a critical role in the **most important** small calibre NATO-qualified military ammunition types used by national armies in the EU as well as in aircraft pyrocartridges that allow the operation of ejection seats in aircraft types that are widely used within and outside the EU

2.2.3.2 Article vs. mixture in a container

Consideration has been given to whether products that contain DBP-based propellants (ammunition and pyrocartridges) should be considered articles under the REACH Regulation or mixtures in containers.

It appears that there has been an on-going debate within the EU explosives industry. Communication with the Association of European Manufacturers of Sporting Ammunition (AFEMS) suggests that in the Association's view, ammunition is an article (AFEMS, 2012). The same belief is apparently held by more than 90% of AFEMS' associated members, although it is recognised that not all ammunition manufacturers agree with this view.

On the other hand, clarification on the issue has been sought from Authorities. A question was submitted to the UK REACH Helpdesk and a response was returned on 26 November 2012[4]. In the Helpdesk's opinion, "*ammunition (bullets, shotgun cartridges, etc.) should be regarded as composite objects. The casing and projectile would be regarded as articles, which together form a container holding the propellant and primer. The propellant and primer are mixtures of substances*".

Following this advice (and associated discussions with officers of ECHA), the applicant has decided to consider the ammunition and the pyrocartridges mixtures of DBP in containers.

Key point 5

This AoA (and the accompanying SEA) assumes that final products that contain DBP-based propellants (finished military and civilian ammunition and finished aircraft pyrocartridges) are mixtures in containers rather than articles

[4] REACH & CLP UK Helpdesk, Helpdesk reference - 2311IRI12-1236.

2.2.4 Tonnage and concentration of DBP in propellant mixtures

2.2.4.1 Tonnage of DBP consumed in the supply chain in the EU

The consumption of DBP by DUs in the applicant's supply chain varies by year and depends on demand for propellant/ammunition by users down the value chain. The latest information available to the authors of this AoA suggests a modest annual consumption, as shown in the CSR (a specific tonnage cannot be provided for reasons of confidentiality).

In general, it can be confirmed that the amount of DBP used in Formulation 2 and Industrial Use 2 is modest and rather niche when seen in the context of the wider uses of the substance. The CSR would suggest that the consumption of DBP in Use 2 represents less than 10% of the consumption of DBP in the applicant's supply chain. The actual consumption in Industrial Use 2 is even lower, as a proportion of the propellant grains are exported to ammunition manufacturers who are located outside the EU.

Predictions on future changes in the consumption of DBP (assuming an Authorisation is granted) are provided in the SEA (Section 1.2.2).

2.2.4.2 Concentration of DBP in propellant mixtures

Information on the DBP content of propellant mixtures and of the final products has been provided by DUs. The concentration of DBP in the propellant mixture varies and depends on the specifications of the different powders. The reason for this variability is that the burning rate of the propellant must be adjusted to fulfil certain ballistic requirements, which differ by propellant product.

Information from literature suggests that the concentration of DBP in propellant formulations varies from >0-10%, but the typical range is 2-5% (Ammunition Pages, undated) (Kubota, 2007) (Olin Winchester Ammunition, 2011) (Kirchner & al, undated) (Ledgard, 2006) (St. Marks Propellants, 1997) (Hunley, 1999). There is broad agreement between the data collected from literature and for consultation. In this AoA, the DBP content of propellants is assumed to be 2-5%.

2.2.4.3 Tonnages of formulations containing DBP

Given the relatively low DBP concentration in propellant mixtures, the overall tonnage of propellants is much more significant than the tonnage of consumed DBP (see Table 1.9 in the SEA). Table 2.3 below shows what percentage of this overall tonnage is represented by propellants used in ammunition of specific calibres/areas of use plus aircraft pyrocartridges.

Table 2.3: Tonnage of DBP-based propellants manufactured in the EU

Propellant category	Tonnage of propellants manufactured (2011)
Small calibre propellants for **civilian** use	20-30% of total
Small calibre propellants for **military** use	70-80%
Medium and large calibre propellants for military use	Small
Propellants for aircraft pyrocartridges	Very small
Source: Consultation *Note: The Table excludes DBP-based propellants for civilian reloading for which an Authorisation is not sought*	

Key point 6

Small calibre ammunition is by far the most important area of use for DBP, particularly for military applications. This is followed in importance by small calibre civilian (competition sport and hobby shooting, and hunting) ammunition

2.3 Conditions of DBP use

2.3.1 Technical parameters of DBP use in propellants

2.3.1.1 Approach to information collection

Whilst the scientific and technical literature has been consulted on the role of moderants and plasticisers such as DBP, the most important source of information has been the current DUs of the substance who have first-hand knowledge of the requirements their propellant mixtures would need to meet. Several written questionnaires and other written and verbal communication have been used in the collection of information on the critical roles of DBP, its functionality in different final products, and the technical feasibility and selection criteria that may be used for a comparison of alternatives to DBP. Consultation begun in October 2011 and finished in April 2013. It must be clear that propellant manufacturers have played a vital role to ensuring the completeness and robustness of this analysis and the authors of this AoA are grateful for the time and effort allocated to answering questions and clarifying issues. Some of the information obtained has not been possible to reproduce due to DU's requests for confidentiality.

2.3.1.2 Technical feasibility and selection criteria for DBP and alternatives

The function of DBP in propellant mixtures is complex and dependent on the final use of the propellant mixtures, in addition to the other constituents of the propellant. Subsequently, when identifying the critical properties of DBP in its use in propellants, it is important that we consider:

1. **critical properties of the substance itself**, which make it suitable for use in the manufacturing process that leads to the formulation of the propellant mixture;
2. **critical properties of the resulting propellant mixture**, which are associated to/depend on the presence of DBP and which need to be achieved in order for the final product (ammunition cartridge, pyrocartridge, etc.) to function as required and prescribed by the end user; and
3. **critical properties of the final product**, which need to be achieved in order for it to be successfully sold on the market and deliver the functionality required by the final user over a minimum time period.

We have thus distinguished three criteria categories and under each one, several technical feasibility and selection criteria have been identified. These are shown in Table 2.4 and are primarily associated with one of the two sub-scenarios of the "Applied for" Use but are, in any case, important to the identification of a substitute for DBP. The main discussion is presented in the Confidential Annex which, among other issues, explains whether it is possible to specify a **threshold level** above or below which any alternative substance could be considered or not to be performing satisfactorily as a substitute for DBP.

Table 2.4: Technical feasibility and selection criteria for the assessment of alternatives

Criteria category	Specific technical feasibility and selection criteria	
Criteria relating to the substance properties and the manufacturing process (Formulation 2)	1	Plasticising effect
	2	Water solubility
Criteria relating to the performance of the propellant and the final product during use (Industrial Use 2)	3	Reduction of burning velocity of the propellant
	4	Diffusion rate
	5	Melting and boiling points
	6	Heat of explosion
Criteria relating to the lifetime of the propellant and the final product (Industrial Use 2)	7	Migration and ballistic shelf-life
	8	Chemical shelf-life
Source: Consultation		

Key point 7

Information received from consultation suggests that the most important criterion for technical feasibility of an alternative is the **ballistic performance of the final ammunition** rather than the alternative moderant/plasticiser meeting a specific threshold for key properties. Ballistic performance needs to be tested in practice rather than be theoretically established, hence the complexity, length and cost of the procedure leading to the substitution of DBP in propellant formulations

The analysis of technical performance criteria in the Confidential Annex suggests that:

- the role of DBP as a moderant in surface treatment of propellant grains shows dependence on the largest number of criteria. This role of DBP is generally the most important, as it is of great significance to the functionality of small calibre propellants, the – by far – most prominent and critical application of DBP-based propellants; and
- water solubility, migration/ballistic shelf-life and chemical shelf-life are criteria that are relevant to all roles/functionalities of DBP.

Key point 8

The property in which DBP particularly excels among its peers, and thus is difficult to replace, is diffusion rate during surface treatment, which is critical for small calibre ammunition propellants

Additional confidential information is presented in: AoA Confidential Annex DBP Propellants DEZA.pdf, Section 2.3.1.2

2.3.1.3 Relevance of technical feasibility criteria to the requirements of the end user

The above discussion primarily reflects the requirements of the propellant manufacturers, as regards the potential substitution of DBP by an alternative substance but also inextricably links to the requirements of the end user which dictate the characteristics and performance of the final product. Consultation suggests that the users of ammunition are primarily concerned with the parameters discussed in the Confidential Annex to this AoA.

Additional confidential information is presented in: AoA Confidential Annex DBP Propellants DEZA.pdf, Section 2.3.1.3

2.3.2 Meeting relevant military and other performance standards

2.3.2.1 Introduction

There are several areas of standardisation (hereafter referred to as 'qualification') for propellants and ammunition and it is imperative that these are taken into account when alternatives to DBP are considered. The purpose of carrying out such qualification is to (a) determine that the propellant and ammunition will remain safe and suitable for service when exposed to the service environment throughout their service lives (including matching the ballistics of the gun); and (b) ensure that relevant Government requirements/directives and national legislation are adhered to (UK Ministry of Defence, 2010).

It should be made clear that the standards generally do not explicitly specify the use of DBP within the final product but rather set out specfic performance characteristics that the final product must meet. The substitution of DBP in the formulation of propellants may be feasible and acceptable from a technical and business perspective, only if the DBP-free formulations and final products can meet the prescribed military and civilian standards. Importantly, the specifications of these standards are not easy to alter in order to accommodate less than suitable alternative components.

2.3.2.2 Standards for propellants and ammunition for military applications

NATO standards

Key NATO structures and concepts of standardisation: the overarching objective of NATO standardisation is to develop concepts, doctrines, procedures, and designs to achieve and maintain the most effective levels of compatibility, interoperability, interchangeability and commonality in the fields of operations, administration and materiel (Pellegrino & Kirkman, 2011). These terms are very important in the operation of the NATO Alliance and are described as follows (Pellegrino & Kirkman, 2011):

- **interchangeability**: items possessing similar functional and physical characteristics that are equal in performance, and capable of being exchanged one for the other without alteration;
- **interoperability**: the ability of systems, units or forces to provide services to and accept services from other systems, units or forces and to use the services exchanged to enable them to operate effectively together; and
- **compatibility**: capability of two or more items or components of equipment or material to exist or function in the same system or environment without mutual interference.

NATO Standardization Agreements for procedures and systems and equipment components, known as "STANAGs", are developed and promulgated by the NATO Standardization Agency in conjunction with the Conference of National Armaments Directors and other concerned authorities[5]. A STANAG is an agreement among several or all member nations to adopt like or similar military equipment, ammunition, supplies and stores, as well as operational, logistic and administrative procedures. The purpose is to allow one member nation's military to use the stores and support of another member's military forces (Pellegrino & Kirkman, 2011). Each NATO member nation ratifies a STANAG and implements it within its military.

[5] Information available at: http://www.nato.int/cps/en/natolive/stanag.htm.

Qualification of the propellant: before a propellant can be placed on the market for use in military ammunition, it needs to be subjected to a qualification procedure. If the composition of the propellant has changed (for example, if DBP is substituted with an alternative substance), the propellant would have to be re-qualified. For a propellant formulation, qualification is an assessment undertaken by a National Authority in accordance with STANAG 4170 and AOP-7 (see description below) aimed at determining whether or not it possesses properties which make it safe and suitable for consideration for use in its intended military role.

STANAG 4170 – Principles and Methodology for the Qualification of Explosive Materials for Military Use

This STANAG lays down important principles of homologation and describes high-level requirements, such as the general safety of propellants (for example, they should not explode if accidentally hit) and the testing that needs to be undertaken (CEN, 2011). STANAG 4170 describes the mandatory data that are required to demonstrate compliance (UK Ministry of Defence, 2010):

a. The explosive composition and its intended role.

b. The characteristics of the explosive material, which are relevant to its intended role and any specific application that is envisaged.

c. The characteristics of the explosive material in its powdered state, as-used condition and after possible degradation due to ageing and the service environment.

d. The effect of thermal ageing, particularly on the safety and performance characteristics of explosive materials. Characteristics of particular interest include thermal, mechanical, and electrostatic discharge sensitiveness, rheological and physical properties.

e. For thermal sensitiveness, the ignition temperature and effects of confinement, charge size and heating rate.

f. In the case of mechanical sensitiveness, the sensitiveness to shock, friction, impact, or to a non-penetrating object, such as a crush or drop, or the effect of confinement and charge size on explosiveness.

g. For electrostatic discharge, the materials sensitiveness to static electricity.

h. The variation of rheological and physical properties with temperature and age of the material.

i. The toxicity and disposal data on the explosive material, its components, and its reaction products, in-so-far-as possible.

NATO member nations agree to a standardised qualification process and each nation has developed their own database of test results (Turner, undated). To qualify, the propellant must undergo all the mandatory testing as well as all additional testing decided by the national Authority. Generally, the number of tests required is particularly large[6].

[6] The Swedish Defence Materiel Administration defines the following mandatory testing : 1. Ignition test, 2. Drop weight impact test, 3. Tear test BAM, 4. Electric spark test, 5. Vessel combustion, 6. Vacuum stability test, 7. DDT test, 8. Combustion temperature, 9. Force. Additional testing may include the following: 1. Ignitability, hot wire, 2.

AOP-7 – Manual of Data Requirements and Tests for the Qualification of Explosive Materials for Military Use

Because of national variations in the testing requirements attached to STANAG 4170, this STANAG is accompanied by **AOP-7**[7], the Manual of Data Requirements and Tests for the Qualification of Explosive Materials for Military Use. This manual documents qualification procedures and tests used by the National Authorities of each member nation to assess the safety and suitability of explosives used in their intended role[8] AOP-7 points to several other STANAGs that describe how each test needs to be undertaken. As noted, tests may differ in each member nation since implementation of STANAG 4170 varies; however, certification according to a STANAG only needs to happen once and is then valid for all countries for which the STANAG applies.

STANAGs other than 4170 that may need to be taken into consideration in the qualification of a propellant[9].

Qualification of the ammunition: the qualification of the propellant is followed by the qualification of the ammunition that contains it. Should the composition of the propellant change, the ammunition will have to be re-qualified as a follow-up to the re-qualification of the propellant.

STANAGs relevant to the qualification of ammunition

There are some very important STANAGs that have to be adhered to, and which would play an important role in the substitution of DBP by potential alternative substances:

- **Small calibre ammunition STANAGs**: the minimum proof and performance requirements for small arms ammunition of NATO calibres are covered in STANAGs as follows:
  - *STANAG 4172 for 5.56 mm calibre*: the 5.56×45 mm NATO (official NATO nomenclature 5.56 NATO) is a rifle cartridge developed in the USA and originally chambered in the M16 rifle. Under STANAG 4172, it is a standard cartridge for NATO forces as well as many non-NATO countries;
  - *STANAG 2310 for 7.62 mm calibre*: the 7.62×51 mm NATO (official NATO nomenclature 7.62 NATO) is a rifle cartridge developed in the 1950s as a standard for small arms among

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Ignitability, laser, 3. Ignitability, propellant fuze, 4. DTA/DSC, 5. Susceptibility to aging, 6. Ignition, hot fragments, 7. Projectile impact test, 8. Steel sleeve test, 9. Detonability test (Swedish Defence Materiel Administration, 1999).

[7] NATO AOP-7: MANUAL OF DATA REQUIREMENTS AND TESTS FOR THE QUALIFICATION OF EXPLOSIVE MATERIALS FOR MILITARY USE (AC/326 SUBGROUP 1). This manual documents Qualification procedures and tests used by the National Authorities of each participating nation to assess the safety and suitability of explosives used in their intended role, e.g. high explosive, booster, etc. The Qualification of a new explosive in accordance with STANAG 4170 and this AOP does not imply Final (or Type) Qualification for use in a specific hardware application (Source: http://engineers.ihs.com/document/abstract/JEFUJBAAAAAAAAAA).

[8] Information available at: http://engineers.ihs.com/document/abstract/JEFUJBAAAAAAAAAA.

[9] *STANAG 4147 – Chemical Compatibility of Ammunition Components with Explosives and Propellants (non-nuclear Applications)*: This includes a series of requirements in Annex B and tests in Annex D, which are to be used to ensure that the chemical compatibility of explosives (propellants) with other ammunition components is at the necessary standard for safety during manufacture, storage and use, and for reliability after storage under approved conditions (information available at http://engineers.ihs.com/document/abstract/WAPWCAAAAAAAAAAA, accessed on 28 July 2013).

NATO member countries. It was introduced to US service in the M14 rifle and M60 machine gun in the late 1950s. The M14 was superseded in US service as the infantry adopted the 5.56×45 mm NATO M16. However, the M14 and many other firearms that use the 7.62×51 mm round remain in service, especially in the case of sniper rifles, machine guns, and as the service weapon chosen by special operations forces. The cartridge is used both by infantry and on mounted and crew-served weapons mounted to vehicles, aircraft and ships;

- *STANAG 4090 for 9 mm calibre*: the 9×19 mm Parabellum cartridge was designed by Georg Luger and introduced in 1902 by the German weapons manufacturer Deutsche Waffen- und Munitionsfabriken (DWM) for their Luger semi-automatic pistol. Under STANAG 4090, it is a standard cartridge for NATO forces as well as many non-NATO countries. It has been described as "*the world's most popular and widely used military handgun cartridge*"; and
- *STANAG 4383 for 12.7 mm calibre*: the 12.7×99 mm NATO (also known.50 Browning Machine Gun (.50 BMG)) is a machine gun/rifle cartridge developed for the Browning .50 calibre machine gun in the late 1910s. Under STANAG 4383, it is a standard cartridge for NATO forces as well as many non-NATO countries. The cartridge itself has been made in many variants: multiple generations of regular ball, tracer, armour piercing, incendiary, and saboted sub-calibre rounds. The 12.7×99 mm cartridge is also used in long-range target and sniper rifles.

These are the so-called "NATO-qualified calibres" and are the most important calibres used in the handguns, rifles and machine guns of the armies of NATO member countries and non-NATO countries (also see Annex 3 to the SEA on the importance of NATO-qualified calibres for the armed and security forces of EU Member States).

- **STANAG 4224 – large calibre artillery and naval gun ammunition greater than 40 mm** (safety and suitability for service evaluation); and
- **other STANAGs:** some Ministries of Defence have been considering the progressive reduction over time of the vulnerability of their stockpile as technology matures and procurement opportunities allow. NATO member countries have agreed a policy for introduction, assessment and testing for Insensitive Munitions. These are prescribed in STANAG 4439 (*STANAG 4439 – Policy for Introduction and Assessment of Insensitive Munitions (IM)*)[10].

Qualification process

Under the above STANAGs, the NATO qualification approval process includes a wide array of tests such as (Pellegrino & Kirkman, 2011):

- precision;
- function & casualty;

[10] Official Insensitive Munitions Policies have been issued by the national authorities in France, Italy, the UK and the USA. The national authorities in Australia, Canada, Denmark, Finland, the Netherlands, Norway and Sweden are considering issuing Insensitive Munition Policies. Information available from http://www.imemg.org/imemg-policies.html (accessed on 13 November 2012).

- EPVAT (Electronic Pressure Velocity and Action Time – thesis a comprehensive procedure for testing ammunition using state-of-the-art instruments and computers);
- trace;
- bullet extraction;
- residual stress;
- penetration waterproof salt spray/corrosion;
- primer sensitivity;
- temp (high/low);
- propellant and primer analysis;
- smoke and flash;
- trajectory match;
- barrel erosion; and
- climatic storage.

For small calibre ammunition, testing requirements for the ammunition are described by the NATO Manual of Proof & Inspection (MOPI) and Multi-Calibre (M-C) MOPI. The MOPI details the tests to be conducted to ensure that the ammunition meets the requirements of the appropriate STANAG and are named as follows:

- 5.56 mm. STANAG 4172 → MOPI AC/225 (LG/3-SG/1) D/8[11];
- 7.62 mm. STANAG 2310 → MOPI AC/225 (LG/3-SG/1) D/9;
- 9 mm. STANAG 4090 → MOPI AC/225 (P111-SP1) D/170(REV); and
- 12.7 mm. STANAG 4383 → MOPI AC/225 (LG/3-SG/1) D/11.

The MOPI prescribes test methods, inspection procedures and equipment needed to perform the subject testing/inspection for the qualification of the ammunition. It includes sample sizes and accept/reject criteria for each test/inspection. The NATO MOPIs are used throughout government/industry and have become the standard for test procedures in the ammunition community. The M-C MOPI was developed to prescribe uniform test procedures across 5.56 mm, 7.62 mm, 9 mm and 12.7 mm ammunition in order to eliminate/reduce inconsistencies and to clarify/simplify procedures (Pellegrino & Kirkman, 2011).

Actors in the qualification process

Qualification for small calibre ammunition (the main area of concern for DBP) at national level is undertaken by National Test Centers (NTCs) which are certified by calibre. NTCs are inspected by the NATO Regional Test Centre Superintendents and staff. There are currently 10 NATO Certified National Test Centers (Pellegrino & Kirkman, 2011):

[11] NATO Army Armaments Group [AC/225] is the sub-group tasked to assess the compliance of candidate ammunition designs with the technical performance requirements defined in the STANAG.

- Belgium (5.56 mm/7.62 mm/9 mm/12.7 mm);
- France (5.56 mm/7.62 mm/9 mm/12.7 mm);
- Germany (5.56 mm/7.62 mm/9 mm);
- Greece (5.56 mm/7.62 mm/12.7 mm);
- Italy (5.56 mm/7.62 mm/9 mm)
- Norway (7.62 mm/12.7 mm);
- Spain (7.62 mm/9 mm); and
- United Kingdom (5.56 mm/7.62 mm/9 mm),

as well as one in Canada (5.56 mm/7.62 mm/9 mm/12.7 mm) and one in the United States of America (5.56 mm/7.62 mm/9 mm/12.7 mm).

Following the qualification of the ammunition at the national level, NATO Qualification Approval follows. NATO Qualification Approval is conducted once for each ammunition design to confirm compliance with the STANAG and MOPI. The ammunition is submitted for qualification to the NATO European Regional Test Centre (ERTC) in Pendine, Wales (UK), which is the recognised facility for the accreditation of small arms and cannon ammunition. Submission is undertaken by a national authority, not the ammunition manufacturer. The submitting NATO nation shall have declared the ammunition design safe and suitable for use by their armed forces and have already procured or produced the ammunition to be tested (Pellegrino & Kirkman, 2011).

After successful completion, a NATO design number is assigned to identify the qualified design. The submitting NATO nation is then granted authority to apply the NATO Symbol of Interchangeability to the outer pack of all ammunition (Swedish Defence Materiel Administration, 1999). It is not possible for manufacturers or non-NATO nations to submit ammunition independently for NATO Qualification Approval testing (Swedish Defence Materiel Administration, 1999).

National authority and company standards

Role of national standards: historically, two categories of national standards have been used in Europe: American ammunition standards and Russian ammunition standards. A significant departure of these standards from the approach of NATO STANAGs is that often specific chemical substances are identified in their specifications. If a propellant manufacturer wants to export its products to several EU Member States (and beyond), they need to check which standards apply to the country of export. If DBP is mentioned in the standards that apply in the destination country, then DBP must be used. For example, US standard MIL-STD-652D clearly mentions DBP as a component of the M1, M6, M31 and M31A1 propellants; therefore, the substance has to be used if the customer requires that the products should comply with said standard.

Examples of national standards include:

- MIL-STD-652C/MIL-STD-652D, Military Standard: Propellants, Solid, for Cannons Requirements and Packing;
- MIL-C-60111C (cartridge, 5.56 mm, military and police design of cartridges); and
- MIL- C-70508 (cartridge, 9 mm, ball, NATO, XM882 (M882)).

The key requirements of these standards are shown in Table 2.5. Notably, other American propellants may also contain DBP. For example, the presence of 2% DBP is required in propellant M14 and the presence of 9% DBP is required in propellant M8 (US Army Defense Ammunition Center, 1998).

Table 2.5: Key requirements of some relevant national standards

<table>
<tr><th>Standard</th><th colspan="5">Relevant excerpts – DBP-related requirements</th></tr>
<tr><td rowspan="2">MIL-STD-652D</td><td>Propellant type</td><td>M1</td><td>M6</td><td>M31</td><td>M31A1</td></tr>
<tr><td>DBP content (%wt)</td><td>5.00 ± 1.00%</td><td>3.00 ± 1.00%</td><td>4.50 ± 0.30%</td><td>5.00 ± 0.30%</td></tr>
<tr><td>MIL-C-60111C</td><td colspan="5">Velocity: the average velocity of the sample cartridges, conditioned at 21° ±1.1°C (70° ±2°F), shall be 3,115 feet per second (ft/sec) plus or minus 40 ft/sec. at 78 feet from the muzzle of the weapon. The standard deviation of the velocities shall not exceed 40 ft/sec.
Chamber pressure: (a) Measurement by copper-crush cylinder: The average chamber pressure of the sample cartridges, conditioned at 21° ±1.1°C, shall not exceed 52,000 pounds per square inch (PSI). The average pressure plus three standard deviations of chamber pressure shall not exceed 58,000 PSI. (b) Measurement by piezoelectric transducer: The average chamber pressure of the sample cartridges, conditioned at 21° ±1.1°C shall not exceed 55,000 PSI. The average chamber pressure plus three standard deviations of chamber pressure shall not exceed 61,000 PSI.
Temperature stability: When the sample cartridges are subjected to the following storage conditions, the average velocity shall not decrease by more than 250 ft/sec and the average chamber pressure by either method used in 3.9 shall not increase by more than 5,000 PSI. Also, the average port pressure by either method above shall neither increase nor decrease by more than 2,000 PSI with respect to the average velocity, chamber pressure and port pressure of the sample cartridges of the same lot, conditioned at 21° ±1.1°C for a minimum of twenty minutes. Any increases in velocity and decreases in chamber pressure of the sample cartridges under these temperature conditions are acceptable.
Stored at 52° ±1.1°C for not less than one hour and fired at that temperature.
Stored at -54°±2.7°C for not less than one hour and fired at that temperature.
Function and casualty: The cartridge shall function without casualty at ambient temperature and under the conditions specified above</td></tr>
<tr><td>MIL- C-70508</td><td colspan="5">Velocity: the average velocity of the cartridges when conditioned at 21°±2°C shall be 385 meters per second (m/sec) plus-or minus 15 m/sec at a point 16 metres from the muzzle. The standard deviation of the velocities shall not exceed 9 m/sec. When conditioned and fired at the following temperatures the average velocity at each temperature shall not vary by more than plus or minus 30 m/sec from the average velocity obtained at 21°C.
-54°± 2°C
+52°± 2°C
Chamber pressure: the corrected average peak chamber pressure of the cartridge at the case mouth position shall not exceed 215 Megapascals (MPa) and no individual peak pressure shall exceed 250 MPa. When conditioned and fired at the following temperatures, the uncorrected average peak chamber pressure at each temperature shall not vary by more than plus or minus 65 MPa from the uncorrected average pressure obtained at 21°C.
-54° ±2°C
+52° ±2°C
Function and casualty: the cartridge shall function in all specified weapons without casualty at ambient temperatures, at -54° ±2°C and +52° ±2°C</td></tr>
<tr><td colspan="6">Sources: Consultation;
US Department of Defense:
http://www.assistdocs.com/search/document_details.cfm?ident_number=30144&StartRow=1&PaginatorPageNumber=1&doc_id=MIL-C-60111C&status_all=ON&search_method=BASIC;
US Department of Defense:
http://www.assistdocs.com/search/document_details.cfm?ident_number=31717&StartRow=50301&PaginatorPageNumber=1007&status_all=ON&search_method=BASIC</td></tr>
</table>

NATO STANAGs vs. national requirements and sales to non-NATO member nations

The qualification of propellants and ammunition that is to be sold to non-NATO countries may vary. There may be cases where EU-based propellant and ammunition manufacturers are able to avoid undertaking a considerable proportion of the tests prescribed by STANAGs. However, it is increasingly the case that non-NATO Ministries of Defence require products sold to them to have been qualified in accordance with the NATO STANAGs. As a result, often the burden of re-qualification is the same irrespective of the location of the customer. With particular regard to the key calibres of 5.56 mm, 7.62 mm, 9 mm and 12.7 mm, these cartridges are so ubiquitous that customers will almost always require NATO-type qualification for products of these calibres.

It should be noted that some standards, such as MIL-C-60111C or MIL-C-70508, may currently be classified as inactive[12]. However, if the customer specifies that the cartridges must meet the requirements of this standard, the propellant/cartridge manufacturers will have to accept this (if they wish to win the contract) and usually there is no space for negotiation on the issue.

Company-specific standards

Examples of company-specific standards have been named by consultees for specific large calibre ammunition and aircraft pyrocartridges. Products have been approved by their users under these company specifications. The details of these standards are not provided here for reasons of confidentiality.

2.3.2.3 Standards for propellants and ammunition for civilian applications

EU Directive 93/15/EEC

Requirements of the Directive: smokeless powder (propellants) must comply with EU Directive 93/15/EEC. The purpose of the Directive is to establish a single market in the EU in the trade of explosives for civilian use. It also aims to harmonise national regulations for civilian explosives and to establish an administrative system for the supervision of transfers of explosives and ammunition. The Directive applies to Class 1 explosives, as listed in the UN Orange Book on the Transport of Dangerous Goods, but does not cover pyrotechnical articles, explosives or ammunition intended for use by the armed forces or police, and other ammunition (**except transfer requirements**).

Explosives falling within the scope of this Directive must comply with the essential safety requirements set out in Annex I. The General Requirements in Annex I are as follows:

1. Each explosive must be designed, manufactured and supplied in such a way as to present a minimal risk to the safety of human life and health, and to prevent damage to property and the environment under normal, foreseeable conditions, in particular as regards the safety rules and standard practices, including until such time as it is used.

2. Each explosive must attain the performance characteristics specified by the manufacturer in order to ensure maximum safety and reliability.

[12] As indicated here: http://www.assistdocs.com/search/document_details.cfm?ident_number=31717&StartRow=50301&PaginatorPageNumber=1007&status_all=ON&search_method=BASIC.

3. Each explosive must be designed and manufactured in such a way that when appropriate techniques are employed it can be disposed of in a manner which minimises effects on the environment.

The Special Requirements are that, as a minimum, the following information and properties – where appropriate – must be considered:

1. Construction and characteristic properties, including chemical composition, degree of blending and, where appropriate, dimensions and grain size distribution.

2. The physical and chemical stability of the explosive in all environmental conditions to which it may be exposed.

3. Sensitiveness to impact and friction.

4. Compatibility of all components as regards their physical and chemical stability.

5. The chemical purity of the explosive.

6. Resistance of the explosive against the influence of water where it is intended to be used in humid or wet conditions and where its safety or reliability may be adversely affected by water.

7. Resistance to low and high temperatures, where the explosive is intended to be kept or used at such temperatures and its safety or reliability may be adversely affected by cooling or heating of a component or of the explosive as a whole.

8. The suitability of the explosive for use in hazardous environments (e.g. environment endangered by firedamp, hot masses, etc.) if it is intended to be used under such conditions.

9. Safety features intended to prevent untimely or inadvertent initiation or ignition.

10. The correct loading and functioning of the explosive when used for its intended purpose.

11. Suitable instructions and, where necessary, markings in respect of safe handling, storage, use and disposal, in the official language or languages of the recipient Member State.

12. The ability of the explosive, its covering, or other components to withstand deterioration during storage until the 'use by' date specified by the manufacturer.

13. Specification of all devices and accessories needed for reliable and safe functioning of the explosive.

Each explosive should be tested under realistic conditions. If this is not possible in a laboratory, the tests should be carried out in the conditions in which the explosive is to be used. Propellants of relevance to DBP must at least also comply with the following requirements:

- they must not detonate when used for their intended purpose; and
- they must be stabilised against decomposition (as they are based on nitrocellulose).

Procedure for attaining CE mark: propellants (not the ammunition) that meet the requirements of the Directive are awarded the CE mark by a Notified Body and then they may be placed on the EU market. Propellants are subject to two procedures by a Notified Body, before they may be placed on the market (BAM, 2012):

- the CE mark examination with verification of conformity to the requirements set out in Annex I of the Directive 93/15/EEC; and
- the monitoring of the quality control system according to one of the modules of the Directive.

The application for CE mark examination has to contain the following information (BAM, 2012):

- exact name of the explosive;
- name and address of the manufacturer or an authorised representative if the manufacturer is not established in the EU;
- a written declaration that the same application has not been lodged with any other Notified Body; and
- a statement regarding which module the quality of the later produced explosive will be guaranteed.

Furthermore, the Notified Body needs (BAM, 2012):

- information on the exact chemical composition of the sample and a suggested composition range for the components, as it will be written in Annex 1 (identification) to the certificate;
- characteristic data, such as density, detonation velocity, grain sizes;
- suitable instructions with respect to safe handling (i.e. intended use, period of usage, storage conditions, and disposal); and
- for the conformity assessment of propellants, the Notified Body requires a sample of 5 kg.

In addition to the CE mark examination, the conformity of the final product to the sample has to be guaranteed. With this aim, a contract on monitoring of quality control with a Notified Body accredited under Directive 93/15/EEC has to be concluded (BAM, 2012).

A list of such bodies is available online[13] and includes 13 organisations located in Belgium, Bulgaria, Czech Republic, Finland, France, Germany, Hungary, Poland, Romania, Slovak Republic, Spain, Sweden and the UK.

Key point 9

Role of Notified Bodies in the re-qualification for propellants for military applications: the CE marking awarded by Notified Bodies recognised under Directive 93/15/EEC is for civilian propellants only. However, Notified Bodies also have to assess propellants for military applications before these are placed on the market. This is to allow their safe transportation. This testing by the Notified Body will attract the usual fee charged for the examination of a civilian propellant for the purposes of CE marking

[13] Available here: http://ec.europa.eu/enterprise/newapproach/nando/index.cfm?fuseaction=directive.pdf&drc_refe_id=12&type_dir=smp&refe_cd=93/15/EEC&drc_desc_v2=93/15/EEC%20Explosives%20for%20civil%20uses (accessed on 18 October 2012).

CIP and SAAMI Standards

The Permanent International Commission (the 'CIP') for the Proof of Small Arms lays down common rules and regulations for the proof of weapons and their ammunition in order to ensure the mutual recognition of Proof Marks by its Member States. Fourteen countries are CIP Member States including Austria, Belgium, Czech Republic, Finland, France, Germany, Hungary, Italy, Slovak Republic, Spain, the UK and also Chile and the United Arab Emirates[14].

In compliance with the 1969 Convention, its Rules and Regulations and CIP Decisions, every small arm together with all highly stressed component parts must undergo lawful testing in the Proof House of the CIP Member State in which the manufacturer is located or, for imported weapons, in the Proof House of the Member State into which they have been imported for the first time. The same applies to commercial ammunition[15].

CIP has progressively established a set of uniform rules for the proofing of firearms and ammunitions to ensure the reciprocal recognition of the proof marks of each of the CIP Member States. It has provided a testing methodology and has prescribed maximum pressure levels. Importantly, the pressure value is connected to the characteristics of the burning propellant, and as explained earlier, DBP affects the burning rate of the propellant. Propellant and ammunition manufacturers need to have due regard of the CIP rules when reformulating and internally testing a civilian propellant/ammunition. As with STANAGs, DBP is not mentioned in CIP's rules; CIP relates to the ballistics of ammunition and the standardisation of guns and has little direct control on the use of specific substances.

Similar to CIP is the Sporting Arms and Ammunition Manufacturers' Institute (SAAMI), an association of American firearms and ammunition manufacturers. SAAMI publishes various industry standards related to the field, including fire code, ammunition and chamber specifications, and acceptable chamber pressure. The primary work of SAAMI is done by its Technical Committee in the setting of industry standards. The Technical Committee works with the CIP, and the CIP and SAAMI are working towards the development of internationally recognised standards. However, SAAMI standards do not always match those of CIP and ammunition manufacturers may need to meet both sets of standards[16].

The propellants manufactured by the users of DBP may need to meet the CIP or SAAMI standards depending on the location they are being marketed in.

2.3.2.4 Standards for aircraft pyrocartridges

Consultation with parties that would be affected by a refused Authorisation for DBP has revealed the complex situation surrounding the re-qualification (also known as 'certification') of reformulated aircraft pyrocartridges.

It has been suggested that it is very hard at the moment to define a complete set of standards. Usually, the aircraft manufacturer in collaboration with the pyrocartridge manufacturer have to make a selection of basic standards and, following that, agree (and complete) them with customer(s)

[14] Yugoslavia was also a member in the past.

[15] Information from the CIP Internet site, http://www.cip-bobp.org/cip.

[16] Information from the SAAMI Internet site, http://www.saami.org/who_we_are/technical/index.cfm.

(the operator of the aircraft, i.e. a national air force) because only standards cited in the contract with the customer shall be considered as relevant and valid.

For the development of new equipment (i.e. a new pyrocartridge), standards are defined usually on the basis of standards used in previous or similar cases. Notably, standards for pyrocartridges, and escape system characteristics are the main requirements, but standards relating to environmental testing have to be included too.

The aircraft manufacturer has provided a list of standards that would potentially be considered in the certification of a new product. This is reproduced in Table 2.6.

Table 2.6: Standards potentially applicable to the re-qualification of new aircraft pyrocartridges

Standard number	Standard title	Associated publications
Safety and performance		
STANAG 4297	STANAG 4297:2001 Guidance on the assessment of the safety and suitability for service of munitions for NATO armed forces - AOP-15	AOP-15 Ed 3: guidance on the assessment of the safety and suitability for service of non-nuclear munitions for NATO armed forces
STANAG 4242 (AECTP-400)	STANAG 4242, Ed. 1 Vibration tests method and severities for munitions carried in tracked vehicles – AOP-34	AOP-34, Ed. 1 Vibration tests method and severities for munitions carried in tracked vehicles
MIL-S-18471G	MIL-S-18471G Military specification: system, aircrew automated escape, ejection seat type: general specification for (08 Jun 1983)	
MIL-C-83125	MIL-C-83125 NOT 1 Cartridges for cartridge actuated/propellant actuated devices, general design specification for	
Environmental testing		
STANAG 4370	STANAG 4370 Ed. 3 (2008) Environmental testing	NATO Allied Environmental Conditions and Test Publication AECTP-400 (Ed 3) Mechanical environmental tests (Jan 2006) NATO Allied Environmental Conditions and Test Publication AECTP-300 (Ed 3), Climatic environmental test (Jan 2006)
MIL-STD-810	MIL-STD-810 Environmental Engineering Considerations and Laboratory Tests	
ISO 2678	ISO 2678:1985 Environmental tests for aircraft equipment - Insulation resistance and high voltage tests for electrical equipment	
Source: Consultation		

Apart from the MILs and STANAGs that are to be met by aircraft pyrocartridges, **all requirements for the escape system of the particular aircraft have to be met**. Throughout the standardisation of ejection seat pyrocartridges, the relevant Military Airworthiness Authority has to be involved.

2.3.3 Practical steps to the re-qualification of propellants and ammunition

The practical steps that would be involved in re-qualification of propellants, ammunition and aircraft pyrocartridges if DBP was to be substituted with an alternative are presented in detail (alongside indication of timelines and associated costs) in the Confidential Annex to this AoA. The

Annex confirms that re-qualification for propellants, ammunition and aircraft pyrocartridges could take several years. Clearly, the number of ammunition products that currently contain DBP is significant and the substitution of DBP would require a lengthy re-qualification period. The associated costs would be several millions of Euros, as described in the Confidential Annex.

Additional confidential information is presented in: AoA Confidential Annex DBP Propellants DEZA.pdf, Section 5.6.1

2.4 Summary of technical requirements for DBP use in propellants

The information presented in the earlier parts of Section 2 is summarised below. This Table provides an overview of the role and functionality of DBP in propellants and outlines the criteria against which the technical suitability of alternatives can be assessed.

Table 2.7: Parameters for DBP use in propellants and assessment of alternatives

Functional aspect	**Explanation**	
Tasks performed by the substance	**Moderant** of propellant combustion, i.e. it delays the burning of nitrocellulose and other energetic components of propellant mixtures **Plasticiser** for processing and shaping (extruding) the propellant, as it influences the rheological properties of the mixture **Coolant**, reducing burning velocity and heat of explosion, thus minimising barrel erosion and other undesirable effects. Of the three functionalities mentioned above, the most important are those of moderant and plasticiser with the former being particularly important for propellants used in small calibre (≤20 mm) ammunition and the latter for propellants used in large (>20 mm) calibre ammunition. Indirectly, DBP allows specific military/civilian ammunition standards to be met	
Physical form of the product	Liquid giving solid propellant grains	
Concentration of the substance in the product	Typically, 2-5% by weight; concentration in the final product (ammunition/pyrocatridge) will be lower	
Critical properties and quality criteria the substance must fulfil	**Criteria for manufacturing process (Formulation 2)**	Plasticising effect
		Water solubility
	Criteria for product performance (Industrial Use 2)	Reduction of burning velocity
		Diffusion rate
		Melting point and boiling points
		Heat of explosion
	Criteria for product lifetime (Industrial Use 2)	Migration and ballistic shelf-life
		Chemical stability and shelf-life
Frequency of substance use and usage quantities	Batch use Quantity depends on composition of mixture; typically 1-10 g DBP per 100 g of nitrocellulose with a typical concentration of 2-5% by weight Overall consumption: varies depending on demand by DUs of propellants; tonnage is shown in the CSR	

Functional aspect	Explanation	
Process and performance constraints concerning the use of the substance	**Temperature**	Variable and confidential. Different propellant types (e.g. single- vs. double- vs. triple-base) need different temperatures. Process temperature may differ among users of DBP because of differences in the technologies used, the mechanical properties of the mixed mass, the solvent used (water or alcohol) and the dosing of DBP. The mixing cannot be made at too high a temperature because of the energetic materials used
	Humidity	Depends on process. When used with a solvent, the mixing process cannot be made in humid conditions because water renders the mixing difficult; the moderant needs to contain <0.1% water
	Purity	The purity of DBP must be higher than 99%
Conditions under which the use of the substance could be eliminated	Use of DBP cannot simply be eliminated from the existing propellant products without substitution by an alternative. Military and civilian ammunition as well as aircraft pyrocartridges could not function without DBP. Therefore, DBP or its entire formulations would have to be substituted with an alternative. Alternative propellant manufactruring technologies which may not use DBP exist; some are established, others are emerging. These technologies are completely alien to the applicant. Furthermore, Annex 7 to the SEA explains that these technologies are not technically or economically feasible for the users of DBP	
Customer requirements associated with the use of the substance	The ammunition used by the Ministries of Defence of NATO member nations (and beyond) must comply with strict military standards, typically dictated by NATO STANAGs; these are very difficult to amend. Ammunition manufacturers require that smokeless powders fulfil specific ballistic behaviour standards and maintain their chemical stability for long-term storage. Thus, propellants are sold on multi-year guarantees, which formulations based on alternative moderants/plasticisers/coolants would also need to meet	
Industry sector and legal requirements for technical acceptability that must be met	Propellants and ammunition for military applications must comply with NATO STANAGs and other national qualification requirements. For propellants, STANAG 4170 is the most critical one. For ammunition, the STANAGs of NATO-qualified calibres (5.56, 7.62, 9 and 12.7 mm) are relevant to the most important propellant grains manufactured with DBP. Propellants for civilian applications need to comply with EU Directive 93/15/EEC and other performance standards (CIP, SAAMI). Substitution of DBP by an alternative substance would result in the re-qualification of the propellants and of all ammunition types that currently contain DBP-based propellants. Re-qualification is lengthy and costly, as explained in the Confidential Annex to this AoA (Section 5.6) and the SEA (Section 2.2)	
Source: Consultation		

3 IDENTIFICATION OF POSSIBLE ALTERNATIVES

3.1 Introduction and scope of analysis

3.1.1 Scope the analysis

Starting the process of generating this AoA, the overall scope of this analysis has included the following possibilities for substitution of DBP in propellant formulations:

- use of alternative non-energetic substances (as explained, DBP is a non-energetic substance);
- use of alternative energetic substances; and
- use of an alternative technology for the manufacture of the propellants.

Nevertheless, there is a requirement to undertake the AoA from the perspective of the applicant, the manufacturer of DBP, DEZA. As a result, the scope of this document has had to be defined as follows:

- **relevance of alternatives to the two sub-scenarios of the "Applied for" Use**: the potential alternative substances analysed in Section 4 of this AoA are relevant to both sub-scenarios describing the "Applied for" Use, thus they are only assessed once. Key reasons for this joint analysis are:
  - for any alternative to be technically and economically feasible to the applicant, it must meet the needs of the processes described under both sub-scenarios; and
  - the performance of DBP in the formulation of propellants and the use of these propellants in ammunition and pyrocartridges are inextricably linked;
- **assessment of feasibility, suitability and availability of alternatives**: the analysis of technical feasibility, economic feasibility and availability are primarily discussed from the perspective of the applicant. However, certain elements are also examined from the perspective of the DUs. These include:
  - technical feasibility – without an alternative being technically feasible for the DUs, there would be no economic incentive for the applicant to manufacture it, as the DUs would not purchase it for use;
  - market availability – it is assumed that wide market availability and presence of established manufacturers/suppliers of the alternatives would reduce the likelihood of the applicant becoming the preferred supplier of the alternatives (thus affecting the economic feasibility of the alternative from their perspective); and
  - R&D to be undertaken by DUs for the identification/development of suitable alternatives – if the DUs do not establish through research whether any (and which specific) alternative substance can deliver the required performance as a substitute for DBP, they would not purchase the alternative and this would affect its economic feasibility from the perspective of the applicant;
- **relevance of potential alternatives to the applicant**: DEZA is a chemicals manufacturer with specialisation in the manufacture of esters, for instance, phthalate esters. DEZA cannot manufacture energetic substances neither can it supply alternative technologies; therefore, the

only alternatives that can be of relevance to the applicant are alternative non-energetic substances.

In light of this, the focus in this AoA is on the analysis of non-energetic substances as suitable to replace one or more of DBP's functions of moderant, plasticiser and coolant. However, other options for substitution, i.e. energetic substances and alternative technologies have also been investigated as a theoretical possibility for DEZA's DUs, in order to provide a complete picture to the decision-maker. Energetic plasticisers and alternative propellant manufacturing technologies are presented in Annex 7 of the SEA.

3.1.2 List of shortlisted potential alternative substances

The next few pages describe the screening process that non-energetic alternatives have undergone. The outcome of the screening process is a shortlist of ten potential alternative non-energetic substances that will be examined in detail in Section 4 of this AoA. The shortlist is given in Table 3.1.

Table 3.1: Alternative substances assessed in detail in the AoA

Potential alternative	EC number	CAS number
1,3-dimethyl-1,3-diphenyl urea (methyl centralite)	210-283-4	611-92-7
1,3-diethyl-1,3-diphenyl urea (ethyl centralite)	201-645-2	85-98-3
1,3-diphenyl urea (Akardite I)	203-003-7	102-07-8
3-methyl - 1,1-diphenyl urea (Akardite II)	236-039-7	13114-72-2
3-ethyl-1,1-diphenyl urea (Akardite III)	242-052-9	18168-01-9
Bis(2-ethylhexyl) adipate) (DEHA)	203-090-1	103-23-1
Acetyl tributyl citrate (ATBC)	201-067-0	77-90-7
Tributyl citrate (TBC)	201-071-2	77-94-1
Dioctyl azelate (DOZ)	203-091-7	103-24-2
Isodecyl pelargonate (IDP)	203-665-7	109-32-0

3.2 Description of efforts made to identify possible alternatives

3.2.1 Research and development activities

3.2.1.1 Activities of the applicant

DEZA has not received any request from customers for alternative chemicals in this particular area of use; the applicant would need a clear indication of technical feasibility from their DUs before it would look into the manufacture of specific substitute chemical substances. As such, no specific targeted need for R&D aimed at identifying a substitute chemical substance has arisen and no R&D has been undertaken by the applicant to date. It is worth noting, however, that DEZA has experience in esterification reactions and is knowledgeable of (but not necessarily experienced in) some of the identified potential products. One of the alternative substances presented in Table 3.1 (DEHA) is currently manufactured by the applicant.

Additional confidential information is presented in: AoA Confidential Annex DBP Propellants DEZA.pdf, Section 4.1.4.

3.2.1.2 Activities of downstream users of DBP

Overview of R&D activities

The authors of this AoA acting on behalf of the applicant conducted extensive consultation with propellant manufacturers. During consultation, we enquired on the R&D work that users of DBP have undertaken towards the identification of a suitable substitute for DBP and the development of alternative propellant mixtures. The R&D that has been undertaken so far has only focused on propellants for ammunition, not for pyrocartridges.

The detail and extent of R&D work that companies have conducted varies, with some of them having spent several years looking for suitable alternatives (having started in the mid- to late-2000s); others may have only recently (2012) started their R&D work. As a result, the amount of time spent and costs incurred so far vary significantly. Specific information by company cannot be provided here due to its commercially sensitive nature.

Companies have been researching both internally (to tap into prior accumulated knowledge and research undertaken internally in the past) and externally (research undertaken by competitors and other experts in the field, and through online searches scouring webpages of companies producing or selling relevant substances). The result of such research has been the identification of a number of candidate substances and a desk-based assessment of their physico-chemical characteristics and their compatibility with other propellant components. Consequently, selected candidate substances may be ordered, delivered and tested in the laboratory. Based on the experience of companies that have already undertaken R&D work, we may distinguish the R&D stages shown in Table 3.2.

Table 3.2: Key steps of on-going R&D for replacing DBP

R&D Stage	Potential alternatives examined at this stage (indicative ranges)	Types of staff involved
Literature review and internal discussion for the selection of potential candidate substitutes for DBP	Up to hundreds	R&D staff, technicians
Assessment of the compatibility of candidate substitutes with the remaining ingredients of the propellant formulation	Up to hundreds	R&D staff, technicians, chem. lab. staff
Laboratory scale testing of the feasibility of incorporation of each candidate substitute into the propellant	<100	R&D staff, technicians, chem. lab. staff, plant operators
Pilot plant scale testing of propellant mixtures that performed sufficiently at the lab test. This includes ballistic tests, ageing tests, etc.	<10	
Industrial scale testing of propellant mixtures, including repeatability testing and in-house qualification testing	Very few	
Source: Consultation		

Duration of R&D and time allocation within downstream user R&D activities

The amount of time that each propellant manufacturer has invested in R&D for replacing DBP varies. As explained above, the earliest that any company has started was in mid-2000s and the most recent has been in 2012. There are cases where R&D is yet to be started; for some companies the importance of DBP-based products within their portfolio of propellants for ammunition is small; hence, it has been difficult for them to justify the expenditure for extensive R&D activities specifically aimed at the substitution of DBP. However, R&D is indeed being undertaken by

several propellant manufacturers who account for the vast majority of the annual consumption of the substance within the applicant's supply chain.

R&D tasks may run concurrently; therefore, literature review and compatibility assessment may be undertaken at the same time throughout the R&D programmes of certain propellant manufacturers. Concurrent delivery of these tasks is essential, as the companies concerned do not have access to large R&D resources. The members of staff involved in R&D are applied researchers who also need to be engaged in other active duties while undertaking R&D on this particular issue. It must also be noted that it is difficult for companies to precisely distinguish between research on a DBP substitute, other research, and other non-research work of the members of staff involved. Some companies may only have a limited number of research staff which often need to be involved in non-research work.

Number of formulations for which alternatives have been investigated (as of end of 2012)

The R&D that has been undertaken so far has covered a variable number of propellant formulations for each company. None of the propellant manufacturers in the applicant's supply chain has looked into all of their propellant formulations yet. As of early 2013, ca. 25% of the combined number of propellant formulations of all affected propellant manufacturers had been investigated. Therefore, not only have propellant manufacturers not been able to identify any suitable alternative to DBP yet, but also any alternative that could be identified or developed might not prove suitable or compatible with their entire product portfolios.

Additionally, it is understood that for companies which may use DBP both as a surface moderant and a plasticiser, the testing that has generally been undertaken so far has focused on the surface treatment of the powder, as finding alternatives for surface treatment is more difficult than for the other functionalities of DBP. Additionally, admixture testing is technically difficult to undertake in the laboratory, as it is neither inexpensive nor quick. Therefore, for the use of DBP in the formulation of propellant grains as a moderant in admixture or as a plasticiser, R&D efforts are generally still lacking.

Cost of downstream user R&D work so far

Information on the cost of R&D work undertaken as of the end of 2012 is provided in the Confidential Annex.

Additional confidential information is presented in: AoA Confidential Annex DBP Propellants DEZA.pdf, Section 5.6.1

3.2.2 Data searches for the purposes of this AoA

A literature review was undertaken by the independent third party who has authored this AoA. The open literature has been searched for information on propellants for the final uses that are of relevance to this AfA. The main approach has been to conduct a general search through a major online search engine and then further elaborate the search terms as new, detailed information was being obtained both from literature and consultation. Information was sought on:

- the identities of potential alternative substances and alternative propellant systems (including acronyms, synonyms, EC numbers and CAS numbers, where available);
- the applicability of potential alternatives to different final uses;
- the technical feasibility, economic feasibility, and human health and environmental hazard properties of potential alternative substances.

Key starting points for the collection of background information have included the following.

Table 3.3: Key information sources used in the identification of potential alternatives

Source	Details	Description
Google	http://www.google.com	Search engine
Google Scholar	http://scholar.google.co.uk	Scientific articles
Google Books	http://books.google.co.uk/bkshp?hl=en&tab=wp	Books
Scirus	http://www.scirus.com/	Scientific search engine

3.2.3 Consultations

3.2.3.1 Key consultees

Extensive consultation was undertaken for the purposes of this AoA. Apart from the manufacturer of DBP, a considerable amount of information, expert advice and insight was provided by several companies active in the applicant's supply chain: propellant manufacturers, a small number of ammunition manufacturers, an aircraft manufacturer and a few selected national Notified Bodies acting under the provisions of Directive 93/15/EEC.

3.2.3.2 Consultation tools

Consultation took several forms:

- **written questionnaires**: several questionnaires and written lists of questions were used for the collection of information. Questionnaires were sent to the applicant in October 2011, May 2012 and June 2013. Questionnaires were disseminated to propellant manufacturers in October 2011, March 2012, May 2012, July 2012, March 2013 and April 2013. A questionnaire was sent to ammunition manufacturers (selected individual companies and trade associations[17]) as well as the manufacturer of the aircraft that uses the DBP-containing pyrocartridges in November-December 2013. The aim of the questionnaires was to collect information on:
  - the usage of DBP in propellants and the associated tonnages and downstream applications;
  - the importance of DBP in the identified applications;
  - the technical feasibility and selection criteria to be used for the assessment of the technical feasibility of potential alternative substances;
  - the technical suitability, economic feasibility and market availability of potential alternative substances;
  - the practical, time and cost implications of re-qualification of propellants and ammunition based on alternative substances;
  - the past and future R&D work that companies have or expect to undertake for the development of alternatives; but also

[17] These included the Association of European Manufacturers of Sporting Ammunition (AFEMS) and the Federation of European Explosives Manufacturers (FEEM).

- the comparison of selected energetic plasticisers to DBP (the information has been used in the preparation of Annex 7 to the SEA);
- the technical feasibility, relevance, economic feasibility and availability of alternative propellant manufacturing technologies and systems (the information has been used in the preparation of Annex 7 to the SEA);

- **face-to-face meetings**: meetings and site visits were held with the applicant and some of the DUs of DBP; and
- **telephone conversations**: when necessary, telephone interviews with individual companies were held.

Other consultation has included the use of a written questionnaire and subsequent email and telephone communication with selected Directive 93/15/EEC Notified Bodies and efforts to communicate with a selected Ministry of Defence, which did not produce a result[18].

Consultation with actors along the supply chain and other stakeholders started in September 2011 and was concluded in July 2013.

3.3 Preliminary assessment and screening of identified non-energetic alternatives

3.3.1 Introduction

The combined approach of consultation and literature review has resulted in the following Table presenting all identified non-energetic substances that might be considered as potential alternatives to DBP.

Table 3.4: Matrix of potential non-energetic alternative substances

No	Substance name	EC Number	CAS Number
1	Dimethyl phthalate (DMP)	205-011-6	131-11-3
2	Diethyl phthalate (DEP)	201-550-6	84-66-2
3	Bis(2-ethylhexyl) phthalate (DEHP)	204-211-0	117-81-7
4	Butyl benzyl phthalate (BBP)	201-622-7	85-68-7
5	Benzyl isononyl phthalate	-	126198-74-1
6	Diamyl phthalate (dipentyl phthalate)	205-017-9	131-18-0
7	Carbamide (urea)	200-315-5	57-13-6
8	Methyl centralite (1,3-dimethyl-1,3-diphenyl urea)	210-283-4	611-92-7
9	Ethyl centralite (1,3-diethyl-1,3-diphenyl urea)	201-645-2	85-98-3
10	Akardite I (1,3-diphenyl urea)	203-003-7	102-07-8
11	Akardite II (3-methyl - 1,1-diphenyl urea)	236-039-7	13114-72-2
12	Akardite III (3-ethyl-1,1-diphenyl urea)	242-052-9	18168-01-9
13	Dipropyl adipate (DPA)	203-371-9	106-19-4

[18] Propellant manufacturers have not condoned approaches to national and transnational (NATO) authorities and invariably did not supply the contact details of relevant contact persons; therefore, no direct input by military authorities has been made to this analysis.

No	Substance name	EC Number	CAS Number
14	Dibutyl adipate (DBA)	203-350-4	105-99-7
15	Di-isobutyl adipate (DIBA)	205-450-3	141-04-8
16	Bis(2-ethylhexyl) adipate (DEHA)	203-090-1	103-23-1
17	Dibutyl sebacate (DBS)	203-672-5	109-43-3
18	Dioctyl sebacate (DOS)	210-829-1	624-10-2
19	Dibutyl maleate (DBM)	203-328-4	105-76-0
20	Acetyl triethyl citrate (ATEC)	201-066-5	77-89-4
21	Acetyl tributyl citrate (ATBC)	201-067-0	77-90-7
22	Acetyl trioctyl citrate (tris(2-ethylhexyl) 2-(acetyloxy) propane-1,2,3-tricarboxylate) (ATOC)	205-617-0	144-15-0
23	Trimethyl citrate (TMC)	216-449-2	1587-20-8
24	Tributyl citrate (TBC)	201-071-2	77-94-1
25	Tris (2-ethyl hexyl) phosphate (TOP)	201-116-6	78-42-2
26	Tricresyl phosphate (TCP)	215-548-8	1330-78-5
27	Camphor	200-945-0	76-22-2
28	Isopropyl myristate	203-751-4	110-27-0
29	Glycerol formal (1,3-dioxan-5-ol & 1,3-dioxolan-4-ylmethanol)	225-248-9 226-758-4	4740-78-7 5464-28-8
30	2,5,7,10-tetraoxaundecane	224-631-8	4431-83-8
31	1,2,3-triacetoxypropane (triacetin)	203-051-9	102-76-1
32	Triphenylamine (TPA)	210-035-5	603-34-9
33	Dioctyl azelate (DOZ)	203-091-7	103-24-2
34	Isodecyl pelargonate (IDP)	203-665-7	109-32-0
35	2,4 dinitrotoluene (2,4-DNT)	204-450-0	121-14-2
36	Tegmer 810 (glycol ester)		-
37	Paraplex G-30 (mixed dibasic acid ester)		-
38	Paraplex G-31 (mixed dibasic acid polyester)		-
39	Paraplex G-50 and G-54 (polyester adipates)	*	
40	Rhodiasolv RPDE (reaction mass of dimethyl adipate and dimethyl glutarate and dimethyl succinate)	906-170-0	-
41	Polymeric sebacate		
42	Novolac epoxy flexibilisers		
43	Silylferrocene polybutadiene-based plasticiser		

Sources: (Sutton, 2001)*;* (US DoD, 2012)*;* (Akhavan, 2011)*;* (Meyer, Koehler, & Homburg, 2002)*;* (Agrawal, 2010)*;* (Toxicology Regulatory Services, 2003)*; Consultation*

** EC numbers and CAS numbers are not available but information is available on the New Jersey Trade Secret Registry Numbers (TSRN) of these products: NJTSRN 8009285003 (Paraplex G-50) and NJTSRN: 8009285034P (Paraplex G-54)*

The Table presents substances representing families of substances such as phthalates, phenyl ureas, citrates, sebacates, adipates, and others. The Table also includes some commercially available (proprietary) mixtures, the composition of which is currently unknown to both the applicant and the propellant manufacturers themselves.

Many of the identified alternatives are accompanied by very little information, other than some basic indication that they might theoretically perform a role similar to that of DBP. This does not

mean that any given potential alternative substance may successfully replace one or more of the functionalities of DBP across all or even some of the current applications of DBP-based propellant formulations.

In the discussion that follows, we have made efforts to separate the three different functionalities of DBP and screen the identified alternatives in terms of technical feasibility for each of the three functionalities. The aim has been to screen out all those alternative substances that are clearly unusable and only focus our detailed analysis (in Section 4 of this AoA) on those (yet unproven ones) that could realistically substitute DBP.

3.3.2 Screening of alternative non-energetic substances

3.3.2.1 Approach

An initial version of this list of the 43 potential alternative non-energetic substances was made available to the manufacturers of propellants in the first questionnaire that was disseminated in October 2011[19]. Companies were asked to provide a comparison between DBP and each potential alternative substance using a range of technical feasibility and selection criteria (those discussed in Section 2.4 of this AoA). Companies were asked to:

- indicate whether they have any practical experience (e.g. have they undertaken any trials and/or R&D work) with each of the alternative substances;
- rank each alternative for technical suitability on a 5-rank scale:
  - (a) *Suitable as a substitute for DBP*;
  - (b) *Suitable but for use alongside DBP or use in certain applications only*;
  - (c) *Promising but uncertain*;
  - (d) *Feasible but poor*;
  - (e) *Unsuitable*.

  For a chemical substance to be considered a potentially suitable alternative, a ranking of (a) to (d) should have been awarded. Particularly, where a (c) ranking ("*Promising but uncertain*") was received, consultees were asked to provide further clarification on the availability of trial/test results and to explain their response in more detail;
- describe key problems that could be faced should any of the potential alternative substances be used as substitutes for DBP;
- compare each alternative to DBP against a set of key technical feasibility and selection criteria[20]. Those used included: (a) reduction of burning velocity, (b) diffusion rate, (c) migration and ballistic shelf-life, (d) heat of explosion, (e) melting and boiling points, (f) chemical stability and shelf-life, (g) solubility in water, and (h) plasticising effect;

[19] Note that a small number of alternative substances were not included in the original list circulated to consultees but were subsequently identified and added to it.

[20] Consultees were also invited to add their own comparison criteria, where appropriate.

- compare each potential alternative to DBP in terms of envisaged usage/consumption rate and cost (per tonne);
- describe the practical, process and other cost implications of adopting each of the potential alternatives; and
- compare each potential alternative to DBP in terms of market availability.

As literature searches and consultation progressed, additional alternative substances were added to the original list and propellant manufacturers were contacted on subsequent occasions with a request to assess the suitability of the new entries.

The applicant also contributed information with regard to current, past and foreseeable future manufacture of any of the identified potential alternative substances (this is presented in the Confidential Annex).

3.3.2.2 Overall technical suitability of non-energetic alternatives

The assessment of the overall technical suitability of the long list of identified potential alternative substances is presented in detail the Confidential Annex. This first initial screening generated a shorter list of potential alternative substances (Table 3.1 and Table 3.2 in the Confidential Annex). A simplified version of Table 3.2 of the Confidential Annex is presented below. This shows the shortlisted potential alternative non-energetic substances. The numbering in the Table refers to the numbering in the previous Table (for consistency).

Table 3.5: Potential non-energetic alternative substances with most favourable technical suitability profile – excludes substances with significant human health hazard concerns

No	Substance (product) name	EC Number	CAS Number
8	Methyl centralite (1,3-dimethyl-1,3-diphenyl urea)	210-283-4	611-92-7
9	Ethyl centralite (1,3-diethyl-1,3-diphenyl urea)	201-645-2	85-98-3
10	Akardite I (1,3-diphenyl urea)	203-003-7	102-07-8
11	Akardite II (3-methyl - 1,1-diphenyl urea)	236-039-7	13114-72-2
12	Akardite III (3-ethyl-1,1-diphenyl urea)	242-052-9	18168-01-9
16	Bis(2-ethylhexyl) adipate (DEHA)	203-090-1	103-23-1
20	Acetyl triethyl citrate (ATEC)	201-066-5	77-89-4
21	Acetyl tributyl citrate (ATBC)	201-067-0	77-90-7
22	Acetyl trioctyl citrate (ATOC)	205-617-0	144-15-0
23	Trimethyl citrate (TMC)	216-449-2	1587-20-8
24	Tributyl citrate (TBC)	201-071-2	77-94-1
27	Camphor	200-945-0	76-22-2
33	Dioctyl azelate (DOZ)	203-091-7	103-24-2
35	Isodecyl pelargonate (IDP)	203-665-7	109-32-0
36	Tegmer 810 (glycol ester)		
37	Paraplex G-30 (mixed dibasic acid ester)		
38	Paraplex G-31 (mixed dibasic acid polyester)		
39	Paraplex G-50 and G-54 (polyester adipates, more generally)		-

Additional confidential information is presented in: AoA Confidential Annex DBP Propellants DEZA.pdf, Section 3.3.2.2.

3.3.2.3 Moderating effect of non-energetic alternative substances

The assessment of the moderating effect of the shorter list of identified potential alternative substances is presented in the Confidential Annex (Table 3.3 and Table 3.4 in the Confidential Annex).

Additional confidential information is presented in: AoA Confidential Annex DBP Propellants DEZA.pdf, Section 3.3.2.3.

3.3.2.4 Plasticising effect of non-energetic alternative substances

The assessment of the plasticising effect of the shorter list of identified potential alternative substances is presented in the Confidential Annex (Table 3.5 and Table 3.6 in the Confidential Annex).

Additional confidential information is presented in: AoA Confidential Annex DBP Propellants DEZA.pdf, Section 3.3.2.4.

3.3.2.5 Cooling effect of non-energetic alternative substances

The assessment of the plasticising effect of the shorter list of identified potential alternative substances is presented in the Confidential Annex (Table 3.7).

Additional confidential information is presented in: AoA Confidential Annex DBP Propellants DEZA.pdf, Section 3.3.2.5.

3.3.3 Conclusion of screening alternative non-energetic substances

The Confidential Annex brings together the results of the above assessments and combines the results in generating the final list of ten non-energetic substances that should be looked at in detail (see Table 3.8 in the Confidential Annex). These include:

1. **acetyl tributyl citrate (ATBC),**
2. **tributyl citrate (TBC)**,

which may theoretically act both as moderants and plasticisers;

3. **methyl centralite (1,3-dimethyl-1,3-diphenyl urea)**,
4. **ethyl centralite (1,3-diethyl-1,3-diphenyl urea)**,
5. **Akardite I (1,3-diphenyl urea)**,
6. **Akardite II (3-methyl - 1,1-diphenyl urea)**,
7. **Akardite III (3-ethyl-1,1-diphenyl urea)**,

which may theoretically be used as moderants of the propellant's burning rate;

8. **bis(2-ethylhexyl) adipate (DEHA)**,

9. **dioctyl azelate (DOZ)**, and

10. **isodecyl pelargonate (IDP)**

which may theoretically be used as propellant plasticisers.

It should be noted again that DBP is used in each case to primarily play only one of its various roles, i.e. it may be used primarily as a moderant or as a plasticiser, depending on the product in question. As a consequence, alternative substances that deliver only one of the two functions might still be considered as potential alternatives **but only for certain of the propellant formulations that currently contain DBP**. The role of moderant is the most important and most relevant to the vast majority of DBP-based propellant formulations.

4 SUITABILITY AND AVAILABILITY OF POSSIBLE ALTERNATIVES

4.1 Introduction

4.1.1 Key sources of information

With regard to the characteristics and properties of potential alternative substances, a range of specialist websites have been consulted. The following Table gives an overview of some of the most important information sources that were used in the preparation of this AoA.

Table 4.1: Key information sources used

Source	Details	Description
Google	http://www.google.com	Search engine
Scirus	http://www.scirus.com/	Scientific search engine
ESIS	http://esis.jrc.ec.europa.eu/home.php	Chemical substance inventory (including old IUCLID files)
ChemPortal	http://www.echemportal.org/echemportal/substancesearch/page.action?pageID=9	Chemical substance inventory
KEMI PRIO Database	http://www2.kemi.se/templates/PRIOEngframes 4144.aspx	Chemical substance inventory
German Federal Environmental Agency List of Substances which are Hazardous to Water	http://webrigoletto.uba.de/rigoletto/public/searchRequest.do?event=request	Inventory of aquatic hazards
SIN List	http://w3.chemsec.org/	Inventory of substances of concern
ChemIDPlus	http://chem.sis.nlm.nih.gov/chemidplus/	Chemical substance inventory
US EPA Substance Registry Services	http://iaspub.epa.gov/sor_internet/registry/substreg/searchandretrieve/substancesearch/search.do	Chemical substance inventory
US EPA High Production Volume Information System (HPVIS)	http://www.epa.gov/hpvis/index.html	Chemical substance inventory and hazard information
New Zealand Inventory of Chemicals	http://www.epa.govt.nz/search-databases/Pages/nzioc-search.aspx	Chemical substance inventory
OECD Screening Information Datasets	http://www.chem.unep.ch/irptc/sids/OECDSIDS/indexcasnumb.htm	Risk assessment information
WHO Environmental Health Criteria Documents	http://www.who.int/ipcs/publications/ehc/en/	Risk assessment information
GESTIS Database of the German Social Accident Insurance	http://gestis-en.itrust.de/nxt/gateway.dll/gestis_en/000000.xml?f=templates$fn=default.htm$3.0	Chemical hazards database
CAMEO Chemicals	http://cameochemicals.noaa.gov/	Chemical hazards database
ATSDR Toxic Substances Portal	http://www.atsdr.cdc.gov/substances/index.asp	Risk assessment information
Syracuse Res. Corp. Database	http://srcinc.com/what-we-do/free-demos.aspx	Risk assessment databases
Environment Canada Lists of Substances	http://www.ec.gc.ca/lcpe-cepa/default.asp?lang=En&n=EE479482-1	Risk assessment information
Australian Hazardous Substances Information System	http://hsis.safeworkaustralia.gov.au/SearchHS.aspx	Risk assessment information
WHO IARC Monographs	http://monographs.iarc.fr/ENG/Classification/index.php	Carcinogenicity effects information

Source	Details	Description
ECETOC Joint Assessment of Commodity Chemicals	http://www.ecetoc.org/jacc-reports	Risk assessment information
TOXNET	http://toxnet.nlm.nih.gov/cgi-bin/sis/search	Human health and environmental data
PubMed	http://www.ncbi.nlm.nih.gov/pubmed	Scientific articles
NLM Gateway	http://gateway.nlm.nih.gov/	Scientific articles
Google Scholar	http://scholar.google.co.uk	Scientific articles
Google Books	http://books.google.co.uk/bkshp?hl=en&tab=wp	Books
ChemSpider	http://www.chemspider.com	Properties of chemical substances
ChemNet	http://www.chemnet.com	Properties of chemical substances
Chemical Book	http://www.chemicalbook.com	Properties of chemical substances

4.1.2 Technical feasibility of selected alternative substances for the applicant

Section 4.1.2 of the Confidential Annex provides an overall analysis of the technical and economic feasibility of the selected potential alternative substances from the perspective of the applicant; in particular, the Confidential Annex discusses in detail the capabilities of the applicant in sourcing the precursors to the shortlisted potential alternatives to DBP and the technical implications of establishing the production of each of the shortlisted substances. Only elements of this analysis, which while taking into account the chemical technology involved is entirely applicant-specific, are presented in this Non-confidential document.

Additional confidential information is presented in: AoA Confidential Annex DBP Propellants DEZA.pdf, Section 4.1.2

a) ALTERNATIVE SUBSTANCE: METHYL CENTRALITE (1,3-DIMETHYL-1,3-DIPHENYLUREA)

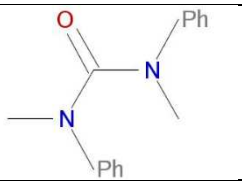
4.2 Methyl centralite

4.2.1 Substance ID and properties

4.2.1.1 Name and other identifiers for the substance

The identity of methyl centralite is presented in the following Table.

Table 4.2: Identity of methyl centralite

Parameter	Value	Source
EC number	210-283-4	1
EC name	1,3-dimethyl-1,3-diphenylurea	1
CAS number	611-92-7	1
IUPAC name	1,3-dimethyl-1,3-di(phenyl)urea	1
Other names	Methyl centralite Carbanilide, N,N'-dimethyl- N,N-Dimethyl-N,N-diphenylurea N,N'-Dimethyl carbanilide N-methyl(methylphenylamino)-N-benzamide Urea, N,Nprime-dimethyl-N,Nprime-diphenyl- Centralite 2 Centralite II	1, 3
Molecular formula	$C_{15}H_{16}N_{20}$	1
SMILES notation	O=C(N(c1ccccc1)C)N(c2ccccc2)C	1
Molecular weight	240.30	1
Structure		2
Sources: *1: ChemSpider Internet site: http://www.chemspider.com/Chemical-Structure.11423.html* *2: ESIS Internet Site: http://esis.jrc.ec.europa.eu/* *3: ACToR Internet site: http://actor.epa.gov/actor/GenericChemical?casrn=611-92-7*		

4.2.1.2 Composition of the substance

No information is available on constituents or impurities. The substance does not appear on ECHA's database of registered substances[21].

[21] Date of last search: 4 July 2013.

4.2.1.3 Physico-chemical properties

The following Table summarises the available information on the physicochemical properties of methyl centralite. Note that the information has been collected from a single literature source and relies heavily on modelling results.

Table 4.3: Physicochemical properties of methyl centralite

Property	Value	Remarks	Source
Physical state at 20°C and 101.3 kPa	Solid	Based on Melting Point of 116-122°C	1
Melting/freezing point	122°C	Predicted	1
	116.54°C	Mean or Weighted MP (EPI Suite)	1
Boiling point	350°C at 101.325 kPa	Predicted data ACD/Labs' ACD/ PhysChem suite	1
	360.11 °C	Adapted Stein & Brown method (EPI Suite)	1
Density	1.161 g/cm^3	Predicted data ACD/Labs' ACD/ PhysChem suite	1
Vapour pressure	0 kPa at 25°C	Predicted data ACD/Labs' ACD/ PhysChem suite	1
	0.190 x 10^{-5} kPa at 25°C	Modified Grain method (EPI Suite)	1
Surface tension	50.54 dyne/cm	Predicted data ACD/Labs' ACD/ PhysChem suite	1
Water solubility	47.37 mg/L at 25°C	Estimate from LogK_{ow} (WSKOW v1.41) - logK_{ow} used: 3.22 (EPI Suite)	1
	11.902 mg/L	Estimate from Fragments: Wat Sol (v1.01) (EPI Suite)	1
Partition coefficient n-octanol/water	3.22	KOWWIN v1.67 estimate (EPI Suite)	1
Flash point	142.635 °C	Predicted data ACD/Labs' ACD/ PhysChem suite	1
Flammability	No data		
Explosive properties	No data		
Self-ignition temperature	No data		
Oxidising properties	No data		
Granulometry	No data		

Source:
1: ChemSpider Internet site: http://www.chemspider.com/Chemical-Structure.11423.html

4.2.1.4 Classification and labelling

An online search was performed using the CAS number in ECHA's C&L Inventory. No information on harmonised classification and labelling for methyl centralite is available. However, one aggregated notification has been made. This is presented in Table 4.4.

Table 4.4: Notified classification and labelling of methyl centralite according to CLP criteria

Classification		Labelling		Number of Notifiers
Hazard Class and Category Code(s)	**Hazard Statement Code(s)**	**Hazard Statement Code(s)**	**Pictograms Signal Word Code(s)**	
Acute Tox. 4 (oral)	H302	H302	GHS07 Wng	1
STOT SE 3 (respiratory system via inhalation)	H335	H335		
Source: *European Chemicals Agency: http://echa.europa.eu/*				

4.2.1.5 REACH Registration details

The following Table summarises the available information on the status of REACH Registration of methyl centralite.

Table 4.5: REACH Registration status of methyl centralite

Registration	Result	Date of last search
Pre-registered	Yes – Envisaged Registration deadline: 30/11/2010	4 June 2012
Registered	No	20 June 2013
Source: *European Chemicals Agency: http://echa.europa.eu/*		

4.2.2 Technical feasibility

4.2.2.1 Technical feasibility from the perspective of the applicant

DEZA does not currently manufacture this substance and does not have any plans to start production in the future without a clear indication from its DUs that methyl centralite would be a technically feasible and acceptable alternative.

The Confidential Annex to this AoA explains that DEZA does not have access to the precursors to methyl centralite and their use by the DEZA plant that currently manufactures DBP is technically infeasible for technical and safety reasons.

Importantly, the manufacture of methyl centralite is based on entirely different technology, which is not within DEZA's capabilities. DEZA's esterification plant can produce a range of phthalates (depending on the availability of precursor alcohols) and other esters, should the raw materials became available, but does not have the ability to manufacture phenyl ureas. Technically, this alternative cannot be considered feasible for the applicant.

Additional confidential information is presented in: AoA Confidential Annex DBP Propellants DEZA.pdf, Section 4.1.2

4.2.2.2 Technical feasibility from the perspective of downstream users

Relevance as substitute for DBP

According to consultation, the relevance of the substance as a substitute for DBP in propellant mixtures is as follows:

Substance family	Dialkyl diphenyl ureas
Function	Moderant

Background to the use of the substance

Functions of methyl centralite in propellants: methyl centralite is used as a stabiliser and a deterrent in propellants and explosives (Harper & Furton, 2007). It also reduces propellant temperature during deflagration and reduces flash in propellants that contain nitro-glycerine (Mirecki & al, 2006). The substance is often described as a stabiliser that also displays a plasticising effect, as shown in the Table below.

Table 4.6: Functionalities of commonly used propellant stabilisers, incl. methyl centralite

Stabiliser categories	**Example substances**
Pure stabilisers	Akardite I
Stabilisers with a gelatinising (plasticising) effect	**Methyl centralite** Ethyl centralite Methyl ethyl centralite Akardite II Substituted urethanes: ethyl- and methylphenylurethanes diphenylurethane
Pure gelatinisers, without a stabilising effect	DBP Diamyl phthalate Camphor
Source: (Meyer, Köhler, & Homburg, 2007)	

A review of the stabilisation of nitrocellulose-based propellants

Generally, the stability of nitrocellulose-based propellants is poor because the stability of nitrocellulose and nitro-glycerine is poor. Smokeless powders containing nitrocellulose or a mixture of nitrocellulose and nitroesters such as nitro-glycerine or diethylene glycol dinitrate are chemically unstable due to the low binding energy (155 $kJ.mol^{-1}$) of the ester functional group $-CH_2O-NO_2$. As a result, gaseous components, especially NO_x, are liberated and nitric and nitrous acids are created during storage and thermal exposure. Gradual decomposition is caused both by the action of residual acids and salts that are usually sealed in nitrocellulose fibres after nitration, and by the general effects of the thermal instability of nitroesters, especially during prolonged exposure or storage. Generated products react with the traces of water and their acidic nature may auto-catalytically accelerate further decomposition (Frys & al, 2010).

Nothing can be done to stop the first degradation reaction (nitrocellulose losing nitrogen oxides), but the second degradation reaction (the newly-formed nitrogen oxides 'attacking' and degrading the nitrocellulose molecule) can be controlled by introducing a chemical stabiliser into the propellant composition (IPI, 2011). As the stabiliser has a greater affinity for the nitrogen oxides than for nitrocellulose, it absorbs the nitrogen oxides before they can degrade the nitrocellulose molecule. Compounds used as stabilisers are mostly substitution products of urea (including methyl centralite) and aromatic amines (e.g. diphenylamine). Readily oxidisable compounds – higher alcohols, camphor, unsaturated hydrocarbons (vaselines) – may also be employed (Meyer, Köhler, & Homburg, 2007).

Methyl centralite is found in double-base propellants, often at a concentration of 5% (Wallace, 2008).

Non-explosive uses of methyl centralite: other uses of methyl centralite include as an ageing retardant for vulcanised rubber (Chemicalland 21, undated-c).

Comparison against key technical feasibility and selection criteria

Trials with the substance and perceived overall technical suitability: this information is presented in the Confidential Annex.

Comparison against the key technical feasibility and selection criteria: this information is presented in the Confidential Annex.

Other technical considerations: consultation with industry experts confirms that there has been substantial research on centralites and other urea-based additives. This research suggests that these substances are not ideal as substitutes for DBP and papers presented at the Fraunhofer Institute for Chemical Technology (ICT) conferences in the period 1995-2004 demonstrate these problems. Key research on the topic has been undertaken by researchers known in the field, Petržílek and Vogelsanger.

During the last few years, the toxicity of stabilisers and their daughter products have become a major issue. At present, all conventional stabilisers (typically, aromatic amines or aromatic urea derivatives, e.g. methyl centralite), which are currently used in nitrocellulose-based gun and rocket propellants, are either toxic by themselves, contain toxic/carcinogenic impurities and/or produce toxic/carcinogenic daughter products (e.g. nitrosamines) during production and/or propellant ageing (Heeb, Langelage, & Vogelsanger, 2008).

A considerable amount of research is being undertaken for the development of a new generation of stabilisers (as will be discussed later in this document) which are not associated with these problems. In light of this on-going research, substances such as methyl centralite would not be ideal substitutes for DBP in nitrocellulose-based propellants.

Additional confidential information is presented in: AoA Confidential Annex DBP Propellants DEZA.pdf, Section 4.2.2.2

4.2.3 Reduction of overall risk due to transition to the alternative

4.2.3.1 Hazard information

Information on the hazards of methyl centralite has been sought from a variety of sources, given that the substance has not been registered in the EU and information from a CSR is not yet available. Information on the nature of the hazards posed by the substance are summarised in Table 4.7, while the mammalian and ecotoxicological hazardous properties are discussed in more detail below.

Table 4.7: Hazard information on methyl centralite

Database	Parameter	Value
German Federal Environmental Agency List of Substances which are Hazardous to Water	Hazard class (Note: there are three water hazard classes (WGK): 1: low hazard to waters 2: hazard to waters 3: severe hazard to waters)	2
Canada Domestic Substance List (DSL) (2007)	Substance category	Organics
	Bioaccumulative	No (rationale: QSAR)
	Persistent	No (rationale: QSAR)
	Inherently Toxic to Aquatic Organisms	No (rationale: QSAR)
	Meets CEPA Categorization Criteria	No
	Meets Environmental Criteria for Categorization	No
	Meets Human Health Criteria	No
	DSL Quantity range (tonnes/year)	0-1

Database	Parameter	Value
NLM TOXNET Toxicology	Journal of Pharmacology and Experimental Therapeutics. Vol. 90, Pg. 260, 1947	LDLo: 500mg/kg (rat)
Sources: (Environment Canada, 2011) *US EPA ACToR Internet site: http://actor.epa.gov/actor/GenericChemical?casrn=611-92-7* *German Federal Environmental Agency Internet site: http://webrigoletto.uba.de/rigoletto/public/searchDetail.do?kennummer=1700#* *LDLo- This is the lowest dose for which data suggests that it may result in the death of an organism, as such the LD_{50} may be assumed to be >500 mg/kg in rats*		

In respect to the Canada Domestic Substance List referred to above, some additional detail is available on the ecological data that were the basis of the conclusions by the Canadian authorities.

Table 4.8: Ecological data supporting decisions of Environment Canada on methyl centralite

Parameter	Value
Persistence	
Media of concern leading to Categorization	Water
Experimental biodegradation half-life (days)	Not available
Predicted ultimate degradation half-life (days)	37.5
Biodegradation (by MITI)	0.0403
Biodegradation (by TOPKAT)	1
Ozone reaction half-life (days) (predicted by EPI)	999
Atmospheric oxidation half-life (days) (predicted by EPI)	0.4122
Underlying data regarding bioaccumulation	
$LogK_{ow}$ predicted by KowWin	3.22
Log BAF T2MTL (predicted by Gobas)	2.038
Log BCF 5% T2LTL (predicted by Gobas)	1.932
Log BCF Max (predicted by OASIS)	2.591
Log BCF (predicted by BCFWIN)	1.781
Aquatic Toxicity	
Pivotal value for iT (mg/L)	3.3
Acute toxicity to fathead minnow (LC_{50} in mg/L) (predicted by TOPKAT v6.1)	3.3
Acute toxicity to fish (LC_{50} in mg/L) (predicted by Ecosar v0.99g)	12.705
Acute toxicity to fish (LC_{50} in mg/L) (predicted by Oasis Forecast M v1.10)	11.484
Acute toxicity to fish (LC_{50} in mg/L) (predicted by PNN)	113.066
Acute toxicity to daphnia (EC_{50} in mg/L) (predicted by TOPKAT v6.1)	224
Acute toxicity to aquatic organisms(fish, daphnia, algae or mysid shrimp) (EC_{50} or LC_{50} in mg/L) (predicted by Ecosar v0.99g)	0.023
Acute toxicity to fish (LC_{50} in mg/L) (predicted by Neutral Organics QSAR in Ecosar v0.99g)	4.23
Chronic toxicity to daphnia or algae (EC_{50} in mg/L) as predicted by Ecosar v0.99g	1.295
Source: OECD Internet site: http://webnet.oecd.org/ccrweb/ChemicalDetails.aspx?ChemicalID=84BA3328-31E8-4225-906A-F5F80C5D30C0 (accessed on 4 July 2013)	

Given the limited dataset on the hazardous properties of methyl centralite, QSAR models (OECD QSAR toolbox and FDA EKDB models) were employed to derive additional insights into both the mammalian and ecotoxicological profile of this substance. The outputs of the modelling (and associated references) are presented in Table 4.9.

Table 4.9: Human health and environmental profile for methyl centralite

Hazard endpoint		Finding	Data source	Study design	Assessed robustness/Comment
Toxicokinetics		96.9%	OECD QSAR	QSAR prediction of human intestinal absorption by Multicase expert system	Result reported to be undefined with regard to domain applicability, hence considered of doubtful reliability
Irritation	Skin irritation/ corrosion	Not corrosive to skin	OECD QSAR	QSAR prediction by Bundesinstitut für Risikobewertung (BfR) skin irritation/corrosion for severe skin irritation	Result reported to be undefined with regard to domain applicability, hence considered of doubtful reliability
		Not corrosive to skin	OECD QSAR	QSAR prediction by BfR skin irritation/corrosion for undefined endpoint	Result reported to be undefined with regard to domain applicability, hence considered of doubtful reliability
		Positive	OECD QSAR	QSAR prediction for severe skin irritation, from Danish EPA database	Reported to be within QSAR domain, hence considered acceptable
	Eye irritation	Unknown	OECD QSAR	QSAR prediction by BfR eye irritation/corrosion	Result reported to be undefined with regard to domain applicability, hence considered of doubtful reliability
Sensitisation		No information			
Genetic toxicity	In vitro - Mutagenicity	Negative	OECD QSAR	QSAR prediction for Ames test (*Salmonella typhimurium*), from Danish EPA database	Reported to be within QSAR domain, hence considered acceptable
		Positive	OECD QSAR	QSAR prediction for DNA reactivity based on Ashby fragments, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
	In vitro – Chromosomal effect	Negative	OECD QSAR	QSAR prediction for sister chromatid exchange in Syrian Hamster Embryo (SHE) assay, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
	In vivo - Mutagenicity	Negative	OECD QSAR	QSAR prediction for Rodent dominant lethal assay, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Negative	OECD QSAR	QSAR prediction for mouse micronucleus assay, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Negative	OECD QSAR	QSAR prediction for *Drosophila melanogaster* sex-linked recessive lethal assay, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
	In vivo – Chromosomal effect	Negative	OECD QSAR	QSAR prediction for mouse micronucleus, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Equivocal	OECD QSAR	QSAR prediction for mouse bone marrow sister chromosome exchange assay, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
Carcinogenicity		Negative	OECD QSAR	QSAR prediction for FDA Cancer Male Mouse, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		TD_{50} = 1000 mg/kg/day	OECD QSAR	QSAR prediction for mouse Carcinogenic Potency Database (CPDB), from Danish EPA	Reported to be within QSAR domain, hence considered acceptable

Hazard endpoint		Finding	Data source	Study design	Assessed robustness/Comment
				Database	
		Negative	OECD QSAR	QSAR prediction for FDA female rat cancer, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Negative	OECD QSAR	QSAR prediction for FDA male rat cancer, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		TD_{50} = 1000 mg/kg/day	OECD QSAR	QSAR prediction for rat Carcinogenic Potency Database (CPDB), from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
Reproductive toxicity		No information			
Developmental toxicity/ Teratogenicity		Negative	OECD QSAR	QSAR prediction from FDA Teratogen Information System (TERIS), from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
Other toxic endpoints	Protein binding potential	No information			
	Androgen receptor binding activity	-1.73 to 2.25 log RBA	FDA EKDB model	Model drew comparison with hydroxylinuron and linuron	Model reports that on basis of only limited similarity with compounds in database (0.46-0.51), no conclusion should be drawn
	Estrogen receptor gene activation	-10000 log RBA	FDA EKDB model	Model drew comparison with Carbendazim, N-Methylaniline and N,N-Dimethylaniline	Model reports that on basis of only limited similarity with compounds in database (0.56-0.60), no conclusion should be drawn
	Estrogen receptor binding activity	Negative	OECD QSAR	QSAR prediction for relative estrogen receptor binding activity, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		-100 to -10000 log RBA	FDA EKDB model	Model drew comparison with 4,4'-Methylenebis(N,N-dimethylaniline), M2 and M1	Model reports that on basis of only limited similarity with compounds in database (0.30-0.37),no conclusion should be drawn
Aquatic Toxicity	Invertebrate	EC_{50} = 0.29 mg/L (48hr)	OECD QSAR	QSAR prediction for *Daphnia magna*, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
	Algael	EC_{50} = 0.439 mg/L (48hr)	OECD QSAR	QSAR prediction for *Pseudokirchneriella subcapitata*, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
	Fish	LC_{50} = 16.2(1.41-185) mg/L (96hr)	OECD QSAR	QSAR prediction for Fathead minnow from the M1 - LC_{50} model	Reported to be within QSAR domain, hence considered acceptable
	Bacteria	EC_{50} = 0.0429 mg/L (5 min)	OECD QSAR	QSAR prediction for *Vibrio fischeri*, from uTOX (Multicase)	Reported to be within QSAR domain, hence considered acceptable

Sources:
OECD QSAR Data obtained using OECD QSAR Toolbox at Internet site:
http://www.oecd.org/chemicalsafety/assessmentofchemicals/theoecdqsartoolbox.htm#Download_qsar_application_toolbox
FDA EKDB data obtained using FDA EKDB Database at Internet site:
http://www.fda.gov/ScienceResearch/BioinformaticsTools/EndocrineDisruptorKnowledgebase/default.htm

Based on all available information, the hazard profile of this substance may be summarised as follows.

Mammalian hazard profile

Acute toxicity: methyl centralite is reported not to meet the Human Health Criteria under the Canada Domestic Substance List, while the available data on estimated acute toxicity (LDLo value in rodents, assumed to refer to oral route) for the substance (Table 4.8) suggest that, were it to be classified under CLP, it may be assumed that it would be considered as no more than a Category 4 acute toxin. Indeed, as can be seen in Table 4.4 of the Non-confidential document, this supports the available notified classification and labelling entry. Although no information has been identified to permit detailed assessment of the justification for the suggested classification for specific target organ toxicity involving the respiratory system via inhalation, the available evidence with regard to the irritancy of the substance suggests this may be warranted.

Repeat dose toxicity: no information is available on the repeat dose toxicity of methyl centralite.

Irritancy and sensitisation: information from literature searches suggests that methyl centralite may cause irritation to skin, eyes and mucous membranes. Prolonged or excessive exposure may cause irritation in sensitive individuals. It is necessary to wear gloves, masks, goggles and use a hood when handling methyl centralite (Chemcas, 2012). In-house QSAR modelling using the OECD toolbox, identified only one prediction drawn from the Danish EPA database considered reliable; this gave a 'Positive' finding for severe skin irritation. No information on sensitisation was identified using the available QSAR models.

Genotoxicity and carcinogenicity: overall the outputs from QSAR modelling, do not raise concerns with regard to either the mutagenic or clastogenic potential of this substance. Methyl centralite has not been assessed by IARC with regard to its carcinogenic potential (IARC, 2013). QSAR modelling identified no concerns with regard to its carcinogenic potential.

Reproductive and developmental toxicity: no published data or QSAR predictions were identified regarding the reproductive toxicity of this substance. A QSAR prediction by the TERIS database indicated it to be negative for developmental toxicity.

Other toxicities: attempts at QSAR modelling of the substance's ability to interact with proteins and with the oestrogen or androgen receptor were largely unsuccessful with no valid conclusions reached using the FDA EKDB model. An OECD QSAR model for oestrogen receptor binding (drawn from the Danish EPA database) did however, report the substance as falling within its domain and to be negative for receptor binding. Thus, at this time, there is no basis for concern regarding methyl centralite's endocrine disruptive potential.

Environmental fate and behaviour and ecotoxicology

Available information, based largely on the outputs of various QSAR models, does not raise concern for either the persistence or bioaccumulative potential of the substance in the environment.

No published experimental ecotoxicity data were identified in the searches conducted for this exercise. While no classification for ecotoxicity has been included in the ECHA C&L Inventory, it is reported as Hazard class 2 in the German Federal Environmental Agency List of Substances that are Hazardous to Water. QSAR modelling of the ecotoxic profile of methyl centralite indicated possible concern with regard to its aquatic toxicity, with predictions of LC_{50} or EC_{50}values <1 mg/L in invertebrate, algal and bacterial species.

4.2.3.2 Comparison of hazards

Comparison to DBP

The following Table compares information available on the hazard profile of methyl centralite with that for DBP. Methyl centralite appears to have a somewhat more benign mammalian toxicological and ecotoxicological profile. Based on the limited QSAR model information available, it would appear that the use of methyl centralite could theoretically reduce the hazards posed to workers and the environment if it substituted DBP; nevertheless, the fact that all risks from the use of DBP in the formulation of propellants and the subsequent use of such propellants have been shown in the CSR to be adequately controlled should be taken into consideration.

Table 4.10: Hazard comparison of DBP and methyl centralite

Hazard endpoint	Methyl centralite	DBP
Human health		
Acute toxicity	Slight (oral)	
Irritancy	Inhalation	
Sensitisation		
Repeat dose		Toxic
STOT		Liver, kidney, testes
Reproductive toxicity		1B (male fertility)
Developmental toxicity		1B (males)
Carcinogenicity		Data are insufficient to determine the carcinogenic potential. No evidence of carcinogenicity is available. The CSR assumes that the substance is not a carcinogen
Environment		
Aquatic	Toxic	Very toxic
Other		
Other issues	Carcinogenic degradation products	
Note: grey cells indicate areas where no relevant information is available		

Concerns about carcinogenic decomposition products

During the last few years, the toxicity of stabilisers and their daughter products has become a major issue. It is known that stabilisers which are currently used in nitrocellulose-based rocket and gun propellants are either toxic by themselves, contain toxic/carcinogenic impurities and/or produce toxic/carcinogenic daughter products during propellant ageing (Wilker, Heeb, Vogelsanger, Petržílek, & Skládal, 2007). In particular, the N-nitrosamines, which can be found in propellants already after production, are known or suspected carcinogens. As a rule of thumb, it can be assumed that the carcinogeneous potential of the N-nitrosamines increases as follows (Wilker, Heeb, Vogelsanger, Petržílek, & Skládal, 2007):

N,N-diaryl-N-NO < N-aryl-N-alkyl-N-NO < N,N-dialkyl-N-NO.

The stabilisers p-nitro-N-methylaniline (pNMA), p-nitro-N-ethylaniline (pNEA), ethyl centralite and methyl centralite, form N-nitroso-N-alkylanilines which are highly carcinogenic. Therefore, it has been stated that these stabilisers should be replaced as soon as practical (Wilker, Heeb, Vogelsanger, Petržílek, & Skládal, 2007). Therefore, whilst centralites may appear to be less

hazardous than DBP, when used in propellant formulations, they may react to give residues of decomposition products. Methyl centralite cannot therefore be considered an ideal alternative for DBP in light of its decomposition behaviour.

4.2.3.3 Safety issues with the manufacture of methyl centralite

The Confidential Annex explains that the use of the precursors to methyl centralite by the applicant would raise serious concerns. Based on hazard classifications and in comparison to the precursors to DBP:

- the carbonyl precursor is acutely toxic (inhalation), may cause skin corrosion and is a hazardous pressurised gas incompatible with the current plant; and
- the amine precursor has more severe acute toxicity properties than the current precursor used by the applicant, is an eye irritant and has high chronic toxicity to the aquatic environment.

The use of precursors to methyl centralite would be unlikely to result in a lowering of existing hazards at the workplace for DEZA's workers.

Additional confidential information is presented in: AoA Confidential Annex DBP Propellants DEZA.pdf, Section 4.1.2

4.2.4 Economic feasibility

DEZA does not and cannot manufacture methyl centralite as it does not have the technology and expertise for doing so. The substance is foreign to DEZA's product portfolio and capabilities.

The Confidential Annex to this AoA explains that the manufacture of methyl centralite could not make use of existing facilities at DEZA's DBP plant. An entire plant rebuild would be required with a cost that could amount to several millions of Euros and would require a timeline sufficiently long to make any thought of starting production completely unrealistic.

Importantly, due to the inherent technical infeasibility of the substance from the perspective of DUs, it is unclear whether any of them would actually use methyl centralite as a substitute for DBP. Even if methyl centralite would prove to be technically feasible for the applicant's customers, the volume of current sales of DBP to propellant manufacturers that could be substituted with methyl centralite would only be very modest, due to (a) the presence of other established suppliers (see Table 4.11) and (b) the overall small tonnage of moderant that is required in the "Applied for" Use.

Overall, if methyl centralite were to be chosen by DUs as a substitute for DBP in propellant formulations, DEZA would lose its entire sales of DBP in the field, as it would not be able to produce this substance. Information on DEZA's turnover that is associated with sales of DBP to propellant manufacturers is provided in the SEA (Section 2.2.2.1).

This alternative substance cannot be considered economically feasible for the applicant.

Additional confidential information is presented in: AoA Confidential Annex DBP Propellants DEZA.pdf, Section 4.1.3

4.2.5 Availability

4.2.5.1 Current and projected availability

Availability for the applicant

As discussed above, methyl centralite is manufactured using technology that is alien to DEZA's current portfolio and capabilities. Phenyl ureas are not possible to manufacture at DEZA's DBP plant, as explained in the Confidential Annex to this AoA.

Availability for the downstream users

Information has been collected from propellant manufacturers and from literature on the market availability of the potential alternative substances. From the perspective of DUs, the majority of alternatives appear to be available on the market but insufficient information has been obtained for some of them. The approach that has been followed and the information that has been collected are presented in the Box below.

For methyl centralite, the available information is given in Table 4.11. The availability of the substance appears to be acceptable but this assertion is based on limited information.

Table 4.11: Market availability of methyl centralite

Alternative	Data availability	Market availability from the perspective of the downstream users
Methyl centralite	Limited	Generally available. Not REACH registered

Box 4.1: Approach to establishing the market availability of potential alternative substances

With regard to the availability of the alternatives from the DUs' perspective, information was sought from two main sources:

- consultation – propellant manufacturers were asked to indicate whether they have researched the market for any of the selected alternatives, whether they are familiar with any suppliers for each of the alternatives and to indicate how confident they are about obtaining the required quantity of alternatives, in the theoretical event that an Authorisation for DBP is not granted; and
- online searches – searches on the Internet were conducted for each of the 10 selected potential alternative substances. The following sources were used to identify companies that may supply the substances in question.

Table A: Chemical distributor databases consulted

Chemical distributor database	Internet link
LookChem	http://www.lookchem.com/
Chemical Book	http://www.chemicalbook.com/
ChemNet	http://www.chemnet.com/
ChemExper	http://www.chemexper.com/
Buyers Guide Chem	http://www.buyersguidechem.com/
ChemIndustry	http://www.chemindustry.com/
Chemical Register	http://www.chemicalregister.com/
Chem Info	http://www.chem-info.com/

4.2.5.2 Actions required for improving availability

Availability for the applicant

For methyl centralite to become available to the applicant a new production line would have to be opened and a new technology introduced.

The Confidential Annex to this AoA explains the challenges that the applicant would face in researching, trialling and starting the production of methyl centralite at their plant. The conclusion is that the availability of the substance for the applicant is very unlikely to improve in the foreseeable future, without very significant investment, which in light of the size of the affected market, cannot be justified.

Additional confidential information is presented in: AoA Confidential Annex DBP Propellants DEZA.pdf, Section 4.1.4

Availability for the downstream users

Methyl centralite is already used in nitrocellulose-based propellant formulations and is generally available on the market for use by propellant manufacturers.

4.2.6 Conclusion on suitability and availability of methyl centralite

4.2.6.1 Technical suitability

The substance is a phenyl urea the manufacture of which is based on precursors and technology completely unknown and wholly incompatible with the applicant's production plant. Methyl centralite cannot be considered technically feasible from the applicant's perspective.

From the perspective of the DUs, the substance could theoretically be used as a moderant but it is a poor plasticiser when compared to DBP and it would not be considered as a potential substitute in propellant formulations where a plasticising effect is specifically needed. The Confidential Annex explains that the substance is not a technically satisfactory substitute for DBP.

Moreover, the association of methyl centralite and other typical stabilisers of nitrocellulose-based propellants with decomposition products that are classified as or are suspected carcinogens casts serious doubts on the technical suitability of the substance, particularly when active efforts have been made to identify alternative, safer stabilisers for nitrocellulose-based propellants.

4.2.6.2 Reduction of overall risks

In a direct comparison to DBP, methyl centralite would appear to have a more benign hazard profile.

The substance does not appear to have been as thoroughly investigated as DBP, yet there are concerns about its irritancy and its effects on the aquatic environment. The issue of its association with hazardous decomposition productions in nitrocellulose-based propellants must also be noted. As the risks from exposure to DBP from its use in the formulation and subsequent use of propellants are adequately controlled, the use of methyl centralite would not result in discernible benefits to DUs' workers' health.

From the perspective of the applicant's workers, the precursors to methyl centralite would appear to have particularly adverse safety and human health hazard profiles and their handling and use would not confer any improvement to the working conditions for the applicant's employees.

4.2.6.3 Economic feasibility

The cost of establishing a production line for methyl centralite would be extremely high and totally unjustified in light of the presence of established suppliers of the substance and the very modest sales that DEZA might potentially achieve in the field of propellants. The lack of documented technical feasibility of the substance from the perspective of the DUs, cannot create optimism that potential sales would allow DEZA to make a profit from a new production line.

4.2.6.4 Availability

From the perspective of the applicant, the substance is not available, as its manufacture is based on technology and precursors which are not available to him. Availability is not expected to improve into the future; the quantity of methyl centralite that would be sold by DEZA is too small to justify the expense of setting up and operating a new production line based on new technology.

On the contrary, for DUs, market availability is believed to be acceptable, as the substance already finds applications in propellant formulations.

Key point 10

Methyl centralite is not a realistic alternative for the applicant and cannot be considered technically or economically feasible

b) ALTERNATIVE SUBSTANCE: ETHYL CENTRALITE

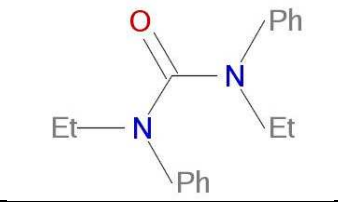
4.3 Ethyl centralite

4.3.1 Substance ID and properties

4.3.1.1 Name and other identifiers for the substance

The identity of ethyl centralite is presented in the following Table.

Table 4.12: Identity of ethyl centralite

Parameter	Value	Source
EC number	201-645-2	2
EC name	1,3-diethyldiphenylurea	2
CAS number	85-98-3	2
IUPAC name	1,3-diethyl-1,3-diphenylurea	1
Other names	Urea, N,N'-diethyl-N,N'-diphenyl- Ethyl centralite Centralite I Centralite 1 Diethyl diphenyl urea N,N'-diethylcarbanilide N-ethyl(ethylphenylamino)-N-benzamide sym-Diethyldiphenylurea Urea, N,Nprime-diethyl-N,Nprime-diphenyl Urea, 1,3-diethyl-1,3-diphenyl-	1
Molecular formula	$C_{17}H_{20}N_2O$	2
SMILES notation	O=C(N(c1ccccc1)CC)N(c2ccccc2)CC	1
Molecular weight	268.35	1
Structure		2
Sources: *1: ChemSpider Internet site : http://www.chemspider.com/Chemical-Structure.6567.html* *2: ESIS Internet site: http://esis.jrc.ec.europa.eu/* *http://www.scbt.com/datasheet-222965-1-3-diethyl-1-3-diphenylurea.html*		

4.3.1.2 Composition of the substance

No information is available on constituents and impurities. The substance is registered at a tonnage range between 100 and 1000 tonnes per year on ECHA's database of registered substances[22].

[22] Date of last search: 25 June 2013.

4.3.1.3 Physico-chemical properties

The following Table summarises the available information on the physicochemical properties of ethyl centralite. The information has been collected from a number of literature sources and consultation.

Table 4.13: Physicochemical properties of ethyl centralite

Property	Value	Remarks	Source
Physical state at 20°C and 101.3 kPa	White to off-white crystalline solid		1, 6
Melting/freezing point	126.45°C	Mean or Weighted MP (EPI Suite)	2
	73-75°C		3
	72°C		6
	71.5-72°C or 79°C	Consultation response	
Boiling point	379 °C at 101.3 kPa	Predicted data ACD/Labs' ACD/ PhysChem suite	2
	383.32°C	Adapted Stein & Brown method (EPI Suite)	2
	326°C	Quoted from Sax´s Dangerous properties of Industrial Materials, 8th ed., 1992	6
	326-330°C	Consultation response	
Density	1.118 g/cm^3	Predicted data ACD/Labs' ACD/ PhysChem suite	2
	1.12 g/cm^3	Quoted from Sax´s Dangerous properties of Industrial Materials, 8th-ed., 1992	6
	1.097g/cm^3		3
Vapour pressure	0 kPa at 25°C	Predicted data ACD/Labs' ACD/ PhysChem suite	2
	2.7 x 10^{-7} kPa (0.00000205 mm Hg)	Quoted from Maylan, 1997	6
	0.86 x 10^{-6}kPa at 25°C	Modified Grain method (EPI Suite)	2
Surface tension	47.92 dyne/cm	Predicted data ACD/Labs' ACD/ PhysChem suite	2
Water solubility	4.791 mg/L at 25°C	Estimate from LogK$_{ow}$ (WSKOW v1.41) (EPI Suite)	2
	1.1208 mg/L	Estimate from Fragments - Wat Sol (v1.01 est) (EPI Suite)	2
	4.79 mg/L at 25°C	Quoted from Maylan, 1997	6
	80 mg/L (80 ppm)		4
Partition coefficient n-octanol/water	4.20	LogK$_{ow}$ (KOWWIN v1.67 estimate) (EPI Suite)	2
	4.2	Quoted from Maylan, 1997	6
Flash point	150.836 °C	Predicted data ACD/Labs' ACD/ PhysChem suite	2
	148.5°C		3
	150°C (302°F)	Quoted from Sax´s Dangerous properties of Industrial Materials (1992)	6
Flammability	Red 1 - Flammability: Must be preheated to burn	Under NFPA 704 NFPA 704 is a standard maintained by the U.S.-based National Fire Protection Association. It defines the colloquial "fire diamond" used by emergency personnel to identify the risks posed by nearby hazardous materials	5
Explosive properties	Yellow 3 -- Reactivity: Strong shock or heat may detonate - use monitors Reactivity Alerts: Explosive		
Self-ignition temperature	No data		

Property	Value	Remarks	Source
Oxidising properties	No data		
Granulometry	No data		
Source: *1: Santa Cruz Biotechnology Internet site: http://www.scbt.com/datasheet-222965-1-3-diethyl-1-3-diphenylurea.html* *2: ChemSpider Internet site: http://www.chemspider.com/Chemical-Structure.6567.html?rid=490247b8-5eff-49be-9f1e-3adbcbd908f0* *3: ChemNet Internet site: http://chemnet.com/Products/supplier.cgi?f=pclist;lang=en;site=chemnet;region=;skey=85-98-3%201%2C3diethyl1%2C3diphenylurea;use_cas=1;rand_id=* *4:* (Wentsel, Wilkinson, Fitzpatrick, Howard, Jones, & Kitchens, 1979) *5: CAMEO Chemicals Internet site: http://cameochemicals.noaa.gov/chemical/20185* *6: European Chemicals Agency: http://echa.europa.eu/*			

4.3.1.4 Classification and labelling

An online search was performed using the CAS number in ECHA's C&L Inventory. No information on harmonised classification and labelling for ethyl centralite is available. However, according to the Inventory, two aggregated notifications have been made which accord with the details on ECHA's REACH registration database. Details are presented in Table 4.14.

Table 4.14: Notified classification and labelling of ethyl centralite according to CLP criteria

Classification		Labelling		Number of Notifiers
Hazard Class and Category Code(s)	**Hazard Statement Code(s)**	**Hazard Statement Code(s)**	**Pictograms Signal Word Code(s)**	
Acute Tox. 4 (oral)	H302	H302 (Harmful if swallowed)	GHS07 Wng	33
Aquatic Chronic 3	H412	H412 (Harmful to aquatic life with long lasting effects)		
		H335 (May cause respiratory irritation)	GHS07 Wng	2
Acute Tox. 4	H302	H302 (Harmful if swallowed)		
Aquatic Chronic 3	H412			
Source: *European Chemicals Agency: http://echa.europa.eu/*				

4.3.1.5 REACH Registration details

The following Table summarises the available information on the status of REACH Registration of ethyl centralite.

Table 4.15: REACH Registration status of ethyl centralite

Registration	Result	Date of last search
Pre-registered	Yes	30 December 2012
Registered	Yes – 100-1,000 t/y	20 June 2013
Source: *European Chemicals Agency: http://echa.europa.eu/*		

4.3.2 Technical feasibility

4.3.2.1 Technical feasibility from the perspective of the applicant

DEZA does not currently manufacture this substance and does not have any current plans to start production in the future without a clear indication from its DUs that ethyl centralite would be a technically feasible and acceptable alternative.

The Confidential Annex to this AoA explains that DEZA does not have access to the precursors to ethyl centralite and their use by the DEZA plant that currently manufactures DBP is technically infeasible for technical and safety reasons.

Importantly, the manufacture of ethyl centralite is based on entirely different technology, which is not within DEZA's capabilities. DEZA's esterification plant can produce a range of phthalates (depending on the availability of precursor alcohols) and other esters, should the raw materials became available, but does not have the ability to manufacture phenyl ureas. Technically, this alternative cannot be considered feasible for the applicant.

Additional confidential information is presented in: AoA Confidential Annex DBP Propellants DEZA.pdf, Section 4.1.2

4.3.2.2 Technical feasibility from the perspective of downstream users

Relevance as substitute for DBP

According to consultation, the relevance of the substance as a substitute for DBP in propellant mixtures is as follows:

Substance family	Dialkyl diphenyl ureas
Function	Moderant (consultation also suggests a particular relevance as a coolant)

Background to the use of the substance

Functions of ethyl centralite in propellants: ethyl centralite serves multiple purposes in solid propellants. It is used as a stabiliser, plasticiser and as a moderant (Harper & Furton, 2007). The substance is often described as a 'stabiliser also offering a plasticising effect', as shown in Table 4.6 (Meyer, Köhler, & Homburg, 2007).

It is found in single-, double- and triple-base propellants (Curtis, 1987), although it is most commonly used in double-base propellants (Wallace, 2008). It may be used as a surface moderant in both small and large calibre ammunition (US EPA, 2012). Ethyl centralite reduces propellant temperature during deflagration and reduces flash in propellants that contain nitro-glycerine (Mirecki & al, 2006). It is also employed as a waterproofing agent for propellants (IPI, 2011).

In propellants, ethyl centralite most often occurs with DPA (diphenylamine) (Wallace, 2008) and finds many military applications (US Army, 1989). Ethyl centralite is also used in propellants for cartridge and propellant actuated devices such as aircraft ejector seats, automotive airbags and seat belt pre-tensioners (SITIS Archives, undated). As a propellant stabiliser, it can be used in relatively large proportions (up to 8%) of the propellant composition (IPI, 2011).

Notably, ethyl and methyl centralite behave in a chemically similar way; however, only one compound is used in the ammunition make up, never both (Croft & Bartley, 2008).

Non-explosive uses of ethyl centralite: the US National Toxicology Program notes a proposed use of the substance in rubber manufacture (US NTP, 2012).

Comparison against key technical feasibility and selection criteria

Trials with the substance and perceived overall technical suitability: this information is presented in the Confidential Annex.

Comparison against the key technical feasibility and selection criteria: this information is presented in the Confidential Annex.

Other technical considerations: as discussed for methyl centralite, conventional stabilisers used for nitrocellulose-based propellants belong to (a) aromatic amines or (b) aromatic urea derivatives. Ethyl centralite belongs to the second group (Frys & al, 2010).

A considerable amount of research is being undertaken for the development of a new generation of stabilisers. It is therefore clear that substances such as ethyl centralite that are considered unsuitable and subject to replacement would not be ideal substitutes for DBP in nitrocellulose-based propellants.

Additional confidential information is presented in: AoA Confidential Annex DBP Propellants DEZA.pdf, Section 4.3.2.2

4.3.3 Reduction of overall risk due to transition to the alternative

4.3.3.1 Hazard information

Information on the hazards of ethyl centralite has been sought from a variety of sources, including the ECHA Dissemination Portal. Information on the nature of the hazards posed by the substance are summarised in Table 4.16, while the mammalian and ecotoxicological hazardous properties are discussed in more detail below.

Table 4.16: Hazard information on ethyl centralite

Database	Parameter	Value
German Federal Environmental Agency List of Substances which are Hazardous to Water	Hazard class (Note: there are three water hazard classes (WGK): 1: low hazard to waters 2: hazard to waters 3: severe hazard to waters)	2
Danish PA Lists of Effects for 2009	Classification	NR50/53;R43
	Vejl. L: The Danish EPA's 'Advisory list for self-classification of dangerous substances' (the Self-classification list)	Yes
Canada Domestic Substance List (DSL) (2007)	Substance category	Organics
	Bioaccumulative	No (rationale: QSAR)
	Persistent	No (rationale: QSAR)
	Inherently Toxic to Aquatic Organisms	Yes (rationale: QSAR)
	Meets CEPA Categorization Criteria	No
	Meets Environmental Criteria for Categorization	No
	Meets Human Health Criteria	No
	DSL Quantity range (tonnes/year)	>1-1,000
NLM TOXNET	National Technical Information Service. Vol. AD277-689	LD_{50} = 200mg/kg, mouse

Database	Parameter	Value
Toxicology	Gigiena i Sanitariya. For English translation, see HYSAAV. Vol. 41(5), Pg. 21, 1976	LD_{50} = 2,500mg/kg, mouse, lungs, thorax, or respiration: cyanosis
		LD_{50} = 2,750mg/kg, rat, lungs, thorax, or respiration: cyanosis
Chemical Carcinogenesis Research Information System	Zeiger, E, Anderson, B, Haworth, S, Lawlor, T and Mortelmans, K (1988): *Salmonella Mutagenicity Tests: IV. Results from the Testing of 300 Chemicals*, Environ. Mol. Mutagen., Vol 11(Suppl.12), pp1-158.	Mutagenicity test (Ames assay in *Salmonella typhimurium*) negative
Sources: (Environment Canada, 2011) *German Federal Environmental Agency Internet site:* *http://webrigoletto.uba.de/rigoletto/public/searchDetail.do?kennummer=4488* *OECD Internet site:* *http://webnet.oecd.org/ccrweb/ChemicalDetails.aspx?ChemicalID=3A98BDE8-609E-410D-9D10-AC01CD64BB5B* *US EPA ACToR Internet site:* *http://actor.epa.gov/actor/GenericChemical?casrn=85-98-3* *Chemical Carcinogenesis Research Information System Internet site:* *http://toxnet.nlm.nih.gov/cgi-bin/sis/search/r?dbs+ccris:@term+@rn+85-98-3*		

In respect of the Canada Domestic Substance List referred to above, additional information is available on the ecological data that were the basis of the conclusions reached by the Canadian authorities.

Table 4.17: Ecological data supporting decisions of Environment Canada on ethyl centralite

Parameter	Value
Persistence	
Media of concern leading to Categorization	Water
Experimental biodegradation half-life (days)	Not Available
Predicted ultimate degradation half-life (days)	37.5
Biodegradation (by MITI)	0.0422
Biodegradation (by TOPKAT)	1
Ozone reaction half-life (days) (predicted by EPI)	999
Atmospheric oxidation half-life (days) (predicted by EPI)	0.3258
Bioaccumulation potential	
Log K_{ow} (predicted by KowWin)	4.2
Log BAF T2MTL (predicted by Gobas)	3.114
Log BCF 5% T2LTL (predicted by Gobas)	2.903
Log BCF Max (predicted by OASIS)	3.522
Log BCF (predicted by BCFWIN)	2.537
Aquatic Toxicity	
Pivotal value for iT (mg/L)	0.963
Acute toxicity to fathead minnow (LC_{50} in mg/L) (predicted by TOPKAT v6.1)	0.963
Acute toxicity to fish (LC_{50} in mg/L) (predicted by Ecosar v0.99g)	1.701
Acute toxicity to fish (LC_{50} in mg/L) (predicted by PNN)	143.300
Acute toxicity to daphnia (EC_{50} in mg/L) (predicted by TOPKAT v6.1)	51.7
Acute toxicity to aquatic organisms(fish, daphnia, algae or mysid shrimp) (EC_{50} or LC_{50} in mg/L) (predicted by Ecosar v0.99g)	0.102
Acute toxicity to fish (LC_{50} in mg/L) (predicted by Neutral Organics QSAR in Ecosar v0.99g)	0.567

Parameter	Value
Chronic toxicity to daphnia or algae (EC_{50} in mg/L) (predicted by Ecosar v0.99g)	0.285
Source: OECD Internet site: http://webnet.oecd.org/ccrweb/ChemicalDetails.aspx?ChemicalID=3A98BDE8-609E-410D-9D10-AC01CD64BB5B	

In addition to the above information sources, QSAR models (OECD QSAR toolbox and FDA EKDB models) were employed to derive additional insight into the mammalian and ecotoxicological profile of this substance. The outputs of the modelling (and associated references) are presented in Table 4.18, overleaf. Based on all available information, the hazard profile of this substance may be summarised as follows:

Mammalian hazard profile

Toxicokinetics: ethyl centralite is reported to be readily absorbed via the gastrointestinal tract and absorption through other relevant tissues (e.g. skin and respiratory tract) may also occur, though has not been quantified (Wentsel, Wilkinson, Fitzpatrick, Howard, Jones, & Kitchens, 1979). However, it is reported to be metabolised in liver though there is no information on its subsequent elimination (ECHA Dissemination Portal).

Acute toxicity: a number of studies have investigated the acute toxicity of ethyl centralite in rodents; the results are summarised in Table 4.19. Some of these suggest an oral LD_{50} value in excess of 2000 mg/kg. However, that reported by Chemische Werke Lowi (1978) indicates a value only one-sixth of this No information on the design of the study by Chemische Werke Lowi (1978) is available but a regulatory compliant study reported on the ECHA Dissemination Portal established an oral LD_{50} in rats of approximately 780 mg/kg bw. In the Weeks & McCreesh (1977) study, male Sprague-Dawley rats were given ethyl centralite in corn oil and clinical signs observed included tremor, lethargy, wet anus, ruffled pelt, red discharge around the eyes, and tonic convulsions at lethal doses. For Korolev *et al* (1976), symptoms observed were characteristic of central nervous system toxicity and cyanosis. The relatively low LD_{50} value that was established for the intra-peritoneal route by Doull *et al.* (1962) would suggest that the low estimate of acute oral toxicity reported by Chemische Werke Lowi might be unreliable.

Table 4.18: Human health and environmental hazard profile for ethyl centralite

Hazard endpoint		Finding	Data source	Study design	Assessed robustness/Comment
Toxicokinetics		97%	OECD QSAR	QSAR prediction of human intestinal absorption by Multicase expert system	Result reported to be undefined with regard to domain applicability; hence considered of doubtful reliability
Irritation	Skin irritation/ corrosion	Not corrosive to skin	OECD QSAR	QSAR prediction by BfR skin irritation/corrosion for severe skin irritation	Result reported to be undefined with regard to domain applicability; hence considered of doubtful reliability
		Not corrosive to skin	OECD QSAR	QSAR prediction by BfR skin irritation/corrosion for an undefined endpoint	Result reported to be undefined with regard to domain applicability; hence considered of doubtful reliability
		Positive	OECD QSAR	QSAR prediction for severe skin irritation, from Danish EPA database	Reported to be within QSAR domain, hence considered acceptable
	Eye irritation	Unknown	OECD QSAR	QSAR prediction by BfR eye irritation/corrosion	Result reported to be undefined with regard to domain applicability; hence considered of doubtful reliability
Sensitisation		No information			
Genetic toxicity	In vitro - Mutagenicity	Negative	CCRIS database, Toxnet databases (in OECD QSAR)	Read-across of Ames Test (*S typhimurium* Strain TA 100) without S9 activation, from Romualdo Benigni	N/A
		Negative	CCRIS database, Toxnet databases (in OECD QSAR)	Read-across of Ames Test (*S typhimurium* Strain TA 153) without S9 activation, from Romualdo Benigni	N/A
		Negative	CCRIS database, Toxnet databases (in OECD QSAR)	Read-across of Ames Test (*S typhimurium* Strain TA 97) without S9 activation, from Romualdo Benigni	N/A
		Negative	CCRIS database, Toxnet databases (in OECD QSAR)	Read-across on Ames Test (*S typhimurium* Strain TA 98) without S9 activation, from Romualdo Benigni	N/A
		Negative	CCRIS database, Toxnet databases (in OECD QSAR)	Read-across on Ames Test *(S typhimurium* Strain TA 100) with S9 activation, from Romualdo Benigni	N/A

Hazard endpoint		Finding	Data source	Study design	Assessed robustness/Comment
		Negative	CCRIS database, Toxnet databases (in OECD QSAR)	Read-across on Ames Test *(S typhimurium* Strain TA 153) with S9 activation, from Romualdo Benigni	N/A
		Negative	CCRIS database, Toxnet databases (in OECD QSAR)	Read-across on Ames Test (*S typhimurium* Strain TA 97) with S9 activation, from Romualdo Benigni	N/A
		Negative	CCRIS database, Toxnet databases (in OECD QSAR)	Read-across on Ames Test (*S typhimurium* Strain TA 98) with S9 activation, from Romualdo Benigni	N/A
		Negative	P&G (in OECD QSAR)	Based on Ames Test (*S. typhimurium* Strain TA 97) without S9 activation, from P&G	N/A
		Negative	P&G (in OECD QSAR)	Based on Ames Test (*S. typhimurium* Strain TA 98) without S9 activation, from P&G	N/A
		Negative	P&G (in OECD QSAR)	Based on Ames Test (*S. typhimurium* Strain TA 100) without S9 activation, from P&G	N/A
		Negative	P&G (in OECD QSAR)	Based on Ames Test (*S. typhimurium* Strain TA 1535) without S9 activation, from P&G	N/A
		Negative	P&G (in OECD QSAR)	Based on Ames Test (*S. typhimurium* Strain TA 1537) without S9 activation, from P&G	N/A
		Negative	P&G (in OECD QSAR)	Based on Ames Test (*S. typhimurium* Strain TA 1538) without S9 activation, from P&G	N/A
		Negative	P&G (in OECD QSAR)	Based on Ames Test (*S. typhimurium* Strain TA 97) with S9 activation, from P&G	N/A
		Negative	P&G (in OECD QSAR)	Based on Ames Test (*S. typhimurium* Strain TA 98) with S9 activation, from P&G	N/A
		Negative	P&G (in OECD QSAR)	Based on Ames Test *(S. typhimurium* Strain TA 100) with S9 activation, from P&G	N/A

Hazard endpoint		Finding	Data source	Study design	Assessed robustness/Comment
		Negative	P&G (in OECD QSAR)	Based on Ames Test (*S. typhimurium* Strain TA 1535) with S9 activation, from P&G	N/A
		Negative	P&G (in OECD QSAR)	Based on Ames Test (*S. typhimurium* Strain TA 1537) with S9 activation, from P&G	N/A
		Negative	P&G (in OECD QSAR)	Based on Ames Test (*S. typhimurium* Strain TA 1538) with S9 activation, from P&G	N/A
		Negative	Kazius et al (in OECD QSAR)	Based on Ames Test (*S. typhimurium*) no information on strain or S9 status, from Kazius et al	N/A
		Negative	OECD QSAR	QSAR prediction by Ames test)*S. typhimurium*), from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Positive	OECD QSAR	QSAR prediction for DNA reactivity based on Ashby fragments, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Equivocal	OECD QSAR	Prediction for sister chromatid exchange assay in mouse bone marrow	Reported to be within QSAR domain, hence considered acceptable
		Equivocal	OECD QSAR	Prediction for sister chromatid exchange assay in mouse bone marrow	Reported to be within QSAR domain, hence considered acceptable
	In vitro – Chromosomal effect	Negative	OECD QSAR	QSAR prediction for sister chromatid exchange in Syrian Hamster Embryo (SHE) assay, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
	In vivo - Mutagenicity	Negative	OECD QSAR	QSAR prediction for Drosophila sex-linked recessive lethal test, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
	In vivo – Chromosomal effect	Negative	OECD QSAR	QSAR prediction for mouse micronucleus assay from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Negative	OECD QSAR	QSAR estimation for Rodent, Dominant lethal assay (chromosome aberration) from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
Carcinogenicity		Negative	OECD QSAR	QSAR prediction for FDA Cancer Female Mouse, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable

Hazard endpoint		Finding	Data source	Study design	Assessed robustness/Comment
		Negative	OECD QSAR	QSAR prediction for FDA Cancer Male Mouse, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		TD50 = 1000 mg/kg/day	OECD QSAR	QSAR prediction for mouse Carcinogenic Potency Database (CPDB), from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Negative	OECD QSAR	QSAR prediction for FDA Cancer Female Rat, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Negative	OECD QSAR	QSAR prediction for FDA Cancer Male Rat, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		TD50 = 1000 mg/kg/day	OECD QSAR	QSAR prediction for rat Carcinogenic Potency Database (CPDB), from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
Toxicity to reproduction	Reproductive	No information			
Developmental toxicity / Teratogenicity		Negative	OECD QSAR	QSAR prediction from FDA Teratogen Information System (TERIS), from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
Other toxic endpoints	Protein binding potential	No information			
	Androgen receptor binding activity	-1.73 to -10000 log RBA	FDA EKDB model	Model drew comparison with hydroxylinuron, p-lactophenetide and linuron	Model reports that on basis of only limited similarity with compounds in database (0.40-0.43), no conclusion should be drawn
	Estrogen receptor gene activation	-10000 log RBA	FDA EKDB model	Model drew comparison with N-ethylaniline, carbendazim and iprodione	Model reports that on basis of only limited similarity with compounds in database (0.46-0.56), no conclusion should be drawn
	Estrogen receptor binding activity	10% RBA	OECD QSAR	QSAR prediction for estrogen receptor binding affinity (Multicase)	Reported to be outside of QSAR domain, hence considered of doubtful reliability
		Negative	OECD QSAR	QSAR prediction by relative estrogen receptor binding activity, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable

Hazard endpoint		Finding	Data source	Study design	Assessed robustness/Comment
		-100 to -10000 log RBA	FDA EKDB model	Model drew comparison with M2, alachlor and hydroxy-flutamide	Model reports that on basis of only limited similarity with compounds in database (0.33-0.35), no conclusion should be drawn
Aquatic Toxicity	Invertebrate	EC_{50} = 0.29 mg/L (48hr)	OECD QSAR	QSAR prediction by immobilization EC_{50} in *D magna*, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
	Bacteria	EC_{50} = 0.0254 mg/L (5 min)	OECD QSAR	QSAR prediction for *V. fischeri*, from uTOX (Multicase)	Reported to be within QSAR domain, hence considered acceptable
Sources: *OECD QSAR Data obtained using OECD QSAR Toolbox at Internet site:* *http://www.oecd.org/chemicalsafety/assessmentofchemicals/theoecdqsartoolbox.htm#Download_qsar_application_toolbox* *FDA EKDB data obtained using FDA EKDB Database at Internet site:* *http://www.fda.gov/ScienceResearch/BioinformaticsTools/EndocrineDisruptorKnowledgebase/default.htm*					

Table 4.19: Acute animal toxicity studies on ethyl centralite

Animal	LD_{50} mg/kg	How administered	Reference
Mice	2,500	Oral	(Korolev, Arsenieva Vitvitskaya, Zakharova, & Kinzinrsky, 1976)
Rat (Wistar)	780.9	Oral	Key study reported on ECHA Dissemination Portal
Rats	2,750	Oral	(Korolev, Arsenieva Vitvitskaya, Zakharova, & Kinzinrsky, 1976)
Rats	420	Oral	(Chemische Werke Lowi, 1978)
Rats	2,560 (1,810-3,160, 95% confidence limit)	Oral	(Weeks & McCreesh, 1977)
Rat	> 198 mg/L	Inhalation (8 hr)	Key study reported on ECHA Dissemination Portal
Rat	>2000 mg/kg/bw	Dermal	Key study reported on ECHA Dissemination Portal
Mice	200	Intra-peritoneal	(Doull, Plzak, & Brois, 1962)
Sources: (Wentsel, Wilkinson, Fitzpatrick, Howard, Jones, & Kitchens, 1979) *European Chemicals Agency: http://echa.europa.eu/*			

As noted in Table 4.10 of the Non-confidential document, the ECHA C&L Inventory database identifies 33 (aggregated) notifications, in which ethyl centralite is given the H302 (Acute Tox. 4 (oral)) precautionary statement. However, via the oral route, clinical signs of neurointoxication (increased neuromuscular irritability, spasm) have been reported. However, the substance is reported not to meet the Human Health Criteria under the Canada Domestic Substance List.

The ECHA Dissemination Portal also reports an inhalation and dermal LD_{50} values in rats of 198 mg/L and >2000 mg/kg bw, respectively based on unidentified studies; the latter value would suggest a low dermal absorption. An acute inhalation study on male Sprague-Dawley rats has also been reported by Weeks & McCreesh (1977) in which groups (6 animals in each) were exposed to untreated air (controls) or air containing ethyl centralite at nominal concentrations of 0.4 or 198 mg/L. For one group receiving each level, the test atmosphere was generated by heating dispersion tubes containing solid compound to 50 or 100°C respectively, while for another group, the dispersion tube was at room temperature (in this latter case there was no discernible loss of test material from the dispersion tube and the nominal concentration of ethyl centralite vapour was 0 mg/L). For all groups, no toxic effects were observed during exposure and a 14-day observation period. At sacrifice, body-weight gain and bodyweight-relative organ weights (for liver, kidney, lung, spleen and testes) were unaffected by treatment and no treatment-related histopathology was observed (nasal turbinates, lung, heart, liver, spleen, oesophagus, stomach, intestines, kidney or testes were examined). These results suggest that ethyl centralite does not represent a significant hazard under conditions of acute inhalation.

Irritancy and sensitisation: An in vitro study using a reconstructed human epidermis model (Guideline B46) conducted to GLP, which concluded the substance to be not irritating, is reported on the ECHA Dissemination Portal. This finding was confirmed by an unidentified study conducted to EU Method B4 and GLP in New Zealand White Rabbits, also reported by this source. Weeks & McCreesh (1977) also report that administration of 0.5 g dry ethyl centralite for 4 hours to intact or abraded skin of New Zealand white rabbits resulted in no irritation after up to 72 hours. Application of 0.5 g in 1.0 mL of acetone vehicle elicited mild irritation by 24 hours. The irritation resolved by 7 days after application.

The ECHA Dissemination Portal reports that ocular irritancy has been assessed in a 2011 study in New Zealand white rabbits conducted to EU Method B5 and GLP in which application of 0.1 g of

the substance was applied to the eye and responses noted for a period of 72 hours, and in a study conducted using Guideline B.47 (Bovine Corneal Opacity and Permeability Test Method for Identifying Ocular Corrosives and Severe Irritant), again to GLP; these found ethyl centralite to be non-irritant. Weeks & McCreesh (1977) also report on the ocular irritancy of this substance. A single application of 0.5 g dry ethyl centralite to one eye of New Zealand white rabbits for 24 hours produced no opacity. However, most of the rabbits exhibited some conjuctival redness and discharge at 24 hours. By 72 hours, the eyes appeared normal, suggesting that the substance is moderately irritating to the eye (Wentsel, Wilkinson, Fitzpatrick, Howard, Jones, & Kitchens, 1979). Use of the OECD QSAR toolbox identified only one positive prediction – in relation to potential severe skin irritancy.

The ECHA Dissemination Portal also reports an unpublished Local Lymph Node Assay (according to EU Method B.42 and GLP) on BALB/c mice in which the substance was tested at levels of 3 to 300 mg/mL, in which no skin reactions or clinical signs were noted and the weight of the ear was not increased, thereby demonstrating it to be not sensitising.

The above data taken together with the entry in ECHA C&L Inventory database of 2 aggregated notifications in which ethyl centralite is assigned a H335 (may cause respiratory irritation) precautionary statement, would suggest that the substance may be capable of eliciting irritancy of the respiratory tract. However, it does not appear to be irritant to the skin or respiratory tract and does not appear to show a dermal sensitisation potential.

Repeat dose toxicity: in a 25-day study on white rats (strain and number unspecified) by Korolev *et al*. (1976), animals were fed a diet containing the substance at 22, 110 or 550 mg/kg for 25 days. None of these animals died during the exposure period but haematological (erythrocyte, leukocyte and reticulocyte counts and levels of haemoglobin and methaemoglobin) and clinical pathological (cholinesterase, aldolase and peroxidase activities, differential blood protein and urinary colour intensity) investigations identified changes in erythrocyte count and peroxidase activity at 110 mg/kg. However, no information was given on the magnitude of this change or the extent to which this was reflective of changes at the high dose level. At sacrifice, organ weights were recorded and liver cholinesterase activity measured. It is reported at that the high dose of 550 mg/kg, changes in a number of parameters were identified ($p<0.05$ - 0.01) but there are no further details given (Wentsel, Wilkinson, Fitzpatrick, Howard, Jones, & Kitchens, 1979). The poor reporting of the study makes interpretation of the toxicological significance of the findings uncertain and unreliable.

Also in Korolev *et al* (1976), white rats were fed a diet containing the substance at levels designed to achieve dosages of 0.05, 0.5 and 5 mg/kg body weight for an unspecified period, but assumed to be longer than the 25-day period addressed in the above experiment. In addition to the parameters assessed in the 25-day study, the following endpoints were also assessed with regard to behaviour (conditioned reflex activity) and clinical pathology (ceruloplasmin and 6-lipoprotein, sulphhydryl groups, and transaminase and phosphatase activity). Semen was also apparently examined. No changes were reported at 0.5 or 0.05 mg/kg bw/d, but statistically significant changes in conditioned reflex activity, liver excretory function, peroxidase activity, ceruloplasmin and sulphhydryl groups were noted at 5 mg/kg bw/d (Wentsel, Wilkinson, Fitzpatrick, Howard, Jones, & Kitchens, 1979). Given the poor level of detail reported on the experimental design and the experimental findings, these findings may be considered unreliable.

Thus, overall, this paper indicated that changes may occur in rodents exposed to repeated dietary dosages of 0.05 mg/kg/d. There is, however, an absence of reliable information with which to establish what constitutes a toxicologically relevant dosage and no reliable NOAEL can be determined. The nature of the fragmentary report available, which does not suggest frank toxicity

was elicited, does however suggest that ethyl centralite may only have limited toxicity under repeat dose conditions.

The ECHA Dissemination Portal reports only one repeat dose study, conducted to EU Method B.7 and GLP, in which Wistar rats were dosed at 0, 50, 150, 450 or 600 mg/kg bw by oral gavage for 28 days, followed for some animals by a period of withdrawal of treatment (recovery phase). Responses to treatment included altered blood ion balance and red cell parameters, decreased blood AST and ASLP activities and, at the high dose, of ALT, together with increase in bilirubin levels. The changes in blood ion balance had not resolved by the end of the recovery period. In females only, signs of neurotoxicity were apparent (Straub phenomenon, restlessness, excitability and extension rigidity of the hindlimbs) during the initial week of treatment only. Increased liver weights of treated animals were noted in both sexes with, in males, histopathological examination identifying hepatic basophile cytoplasm and cortical dystrophy of the kidneys. In females, hyperplasia of ovarian stromal interstitial cells and genital tract hydrometra of the uterus were noted. A LOEL (Lowest Observed Effect Level) of 50 mg/kg/day that applied to both sexes was established. The authors suggest that the changes observed are without toxicological importance and adaptive in nature but provide no robust argumentation to support this conclusion; the ECHA Dissemination Portal also notes that the conduct of a 90 day study in rodents is being considered.

Genotoxicity and carcinogenicity: in the poorly reported and unreliable paper referred to above, Korolev *et al* (1976) reported no mutagenic effects. Weeks & McCreesh (1977) and Wentsel et al (1979) report negative findings from Ames assays on *Saccharomyces cerevisiae*. In an Ames assay by Mortelmans & Zeiger (2000), in which S. typhimurium strains TA100, TA1535, TA97 and TA98 were tested with and without metabolic activation, no effect was identified. The ECHA Dissemination Portal also presents an unpublished mouse lymphoma L5178Y cell assay conducted to EU Method B.17 and OECD 476 and to GLP, and an unpublished in vitro chromosome aberration test in human lymphocytes conducted to EU Method B.10 and GLP; both studies were negative.

A series of QSAR predictions were obtained from the OECD toolbox; of those considered to fall within the domain of the respective model, only a prediction for DNA reactivity based on Ashby fragments indicated positive genotoxic activity. Equivocal findings were also reported for sister chromosome exchange in a mouse bone marrow model. A series of within-domain QSAR model estimates of carcinogenic potential indicate low concern with regard to the potential for carcinogenicity and, overall, therefore there appears to be little concern with regard to either the potential genotoxic or carcinogenic potential of the substance.

Reproductive and developmental toxicity: in an unpublished Reproduction and Developmental Toxicity Screening Test (OEC421) conducted to GLP reported on the ECHA Dissemination Portal, Wistar rats were given the substance by oral gavage at dosages of 50, 150 or 450 mg/kg bw. A NOAEL of 450 mg/kg bw/d was established in both the parental and F1 generations. However, in the detailed description of the study findings it is noted that signs of neurotoxicity were observed during the initial week of treatment and that one female of the parental generation given the high dosage died following the first administration. However, none of the reproductive or developmental parameters assessed were adversely affected by treatment. No other information is available on the reproductive toxicity of the substance. The TERIS database does, however, suggests it is not a developmental toxicant.

Other toxicities: robust QSAR modelling of the substance's ability to interact with the oestrogen receptor or gene, or the androgen receptor was possible. However, the outputs derived do not raise particular concern.

Environmental fate and behaviour and ecotoxicology

Ethyl centralite is reported to have a solubility of 80 ppm suggesting that it would initially occur in water; however, given its high organic solubility it would be expected to be readily adsorbed onto sediment (Wentsel, Wilkinson, Fitzpatrick, Howard, Jones, & Kitchens, 1979). However, other sources dispute this water solubility figure, suggesting much lower values (see Table 4.9 of the Non-confidential document).

Furthermore, the substance is resistant to acid and base hydrolysis, though where the chemical is degraded, the resulting products have been suggested to be N-ethylaniline and carbon dioxide (Wentsel, Wilkinson, Fitzpatrick, Howard, Jones, & Kitchens, 1979). No information has been identified on photodegradability. However, as assessed by the registrant on the ECHA Dissemination Portal, ethyl centralite is judged to be neither PBT, nor vPvB.

The ECHA Dissemination Portal reports a GLP compliant 96-hr static test conducted to Guideline Letale Wirkung beim Zebrabärbling-*Brachydanio rerio* (LC 0, LC 50, LC 100; 48-96 Stunden) Verfahrensvorschlag: Umweltbundesamt Berlin, Stand Mai 1984), in *Danio rerio* in which a LC_{50} of 15.6 mg/L was estimated. An Algal Inhibition Test to EU Guideline C.3 and GLP on *Desmodesmus subspicatus* is also reported that gave a 72 hour ErC_{50} of 37.8 mg/L (average exposure concentration; 95% confidence limit: 36.09 – 39.42 mg/L).

Considering other published data, Wentsel *et al* (1979) report that ethyl centralite is acutely toxic to fish at 10 ppm and that a level of 5 ppm is sufficient to rapidly stress fish. Additional information on the substance's toxicity to fish is available from the study '*Lethal Effects of 1888 Chemicals upon Four Species of Fish from Western North America*' (MacPhee & Ruelle, 1969). This study reports a series of 24 hour screening assays on multiple chemicals in the following fish species - northern squawfish (*Ptychocheilus oregonenm*), chinook salmon (*Onchorhynchus tshawytscha*), coho salmon (O. *kzxutch*) and the steelhead (*Salmo gairdnen*), with effects assessed in terms of mortality or loss of equilibrium. For ethyl centralite, death was noted to occur after 1-3 hours of exposure at 10 ppm suggesting it has a moderate to high aquatic toxicity; a NOAEL was not defined by the study. Furthermore, OECD QSAR predictions of the acute toxicity in bacteria and invertebrate species also suggest a significant level of aquatic toxicity.

Together, these data suggest that ethyl centralite is of moderate to high aquatic toxicity and this opinion is supported by the concerns identified by German and Danish authorities (see Table 4.16). The ECHA Dissemination Portal reports a $PNEC_{freshwater}$ of 0.0143 mg/L and a $PNEC_{freshwater\ sediment}$ of 0.784 mg/kg dryweight. For marine waters, values are $PNEC_{marine\ water}$ are 0.143 mg/L and $PNEC_{marine\ sediment}$ of 0.791 mg/kg dryweight.

In the 35 aggregated notifications on the ECHA C&L Inventory database, it is given a H412 (Aquatic Chronic 3) precautionary statement.

Limited insight into the consequences of exposure to the substance on terrestrial species is available from a study on house and deer mice (*Mus musculus* and *Peromyscus maniculatus*, respectively) (Schafer & Bowles, 1985). The LD_{50} in deer mice was found to be 1125 mg/kg bw (again suggestive of relatively low mammalian toxicity; see discussion on acute toxicity in mammals above) and a reduction in food intake of 10.0% was noted in this species when given a diet of wheat seeds treated with 2% of the test substance over a 3-day test period. For the house mouse, 40% of animals were found to refuse to eat more than 50% of the provided wheat seeds when they were treated with 2% of the test substance over a 5-day test period. This study suggests that, at least in murine species, exposure to a diet containing the substance would lead to avoidance responses.

4.3.3.2 Comparison of hazards

Table 4.20 compares the hazard profile of ethyl centralite with that of DBP, in terms of their proposed DNELs. As can be seen, currently the DNELs proposed for ethyl centralite by its registrant for long-term dermal exposure dermal of workers are more stringent than those for DBP, as are the long-term inhalation and oral DNELs for the general population.

Table 4.20: Human health risk comparison between ethyl centralite and DBP

Parameter	Ethyl centralite		DBP	
Workers				
Acute / short-term exposure - systemic effects	Dermal DN(M)EL		Dermal DN(M)EL	
	Inhalation DN(M)EL		Inhalation DNEL	2.84 mg/m³
Acute / short-term exposure - local effects	Dermal DN(M)EL		Dermal DN(M)EL	
	Inhalation DN(M)EL		Inhalation DN(M)EL	
Long-term exposure - systemic effects	Dermal DNEL	0.0556 mg/kg bw/day	Dermal DNEL	0.19 mg/kg bw/day
	Inhalation DNEL	0.1959 mg/m^3	Inhalation DNEL	0.13 mg/m³
Long-term exposure - local effects	Dermal DN(M)EL		Dermal DN(M)EL	
	Inhalation DN(M)EL		Inhalation DN(M)EL	
General population				
Acute / short-term exposure - systemic effects	Dermal DN(M)EL		Dermal DN(M)EL	
	Inhalation DN(M)EL		Inhalation DN(M)EL	
Acute / short-term exposure - local effects	Dermal DN(M)EL		Dermal DN(M)EL	
	Inhalation DN(M)EL		Inhalation DN(M)EL	
Long-term exposure - systemic effects	Dermal DNEL		Dermal DNEL	2.2 mg/kg bw/day
	Inhalation DNEL	0.0483 mg/m³	Inhalation DNEL	0.62 mg/m³
	Oral DNEL	0.0278 mg/kg bw/day	Oral DNEL	0.22 mg/kg bw/day
Long-term exposure - local effects	Dermal DN(M)EL		Dermal DN(M)EL	
	Inhalation DN(M)EL		Inhalation DN(M)EL	

Sources:
CSR
European Chemicals Agency: http://echa.europa.eu/
Note that for the general population, the CSR does not include toxicological thresholds, as consumer exposure is not considered relevant to the uses of the substance. The figures noted above in the grey part of the Table are from the registration of DBP, as shown on the ECHA Dissemination Portal

Table 4.21 compares the environmental hazard profile of ethyl centralite with that of DBP, in terms of their proposed PNECs. The values for DBP are considerably more stringent than those for ethyl centralite.

Table 4.21: Environmental risk comparison between ethyl centralite and DBP

Parameter	Ethyl centralite		DBP	
Aquatic organisms				
Freshwater	PNEC aqua (freshwater)	0.0143 mg/L	PNEC aqua (freshwater)	10 µg/L
Marine water	PNEC aqua (marine water)	0.143 mg/L	PNEC aqua (marine water)	1 µg/L
Intermittent releases	PNEC aqua (intermittent releases)	0.143 mg/L	PNEC aqua (intermittent releases)	
STP	PNEC STP	10 mg/L	PNEC STP	0.22 mg/L
Sediment (freshwater)	PNEC sediment (freshwater)	0.784 mg/kg sediment dw	PNEC sediment (freshwater)	1.19 mg/kg sediment dw
Sediment (marine water)	PNEC sediment (marine water)	0.791 mg/kg sediment dw	PNEC sediment (marine water)	0.119 mg/kg sediment dw
Air				
Air		No hazard		No hazard
Terrestrial organisms				
Soil	PNEC soil	0.174 mg/kg soil dw	PNEC soil	0.05 mg/kg soil dw
Predators				
Secondary poisoning	PNEC oral	30 mg/kg food	PNEC oral	1.33 mg/kg food
Sources: *CSR* *European Chemicals Agency: http://echa.europa.eu/*				

Table 4.22 considers the underlying hazard profiles of the two substances in more detail, and indicates that ethyl centralite may show a somewhat more benign profile in mammals, at least with regard to its reproductive and developmental toxic profile. There is, however, a degree of uncertainty with regard to its repeat dose toxicity since a LOAEL, but no NOAEL, has been established based on effects in several organ systems; it is understood that further investigation of this aspect has been proposed by the registrant. Nonetheless, based on the currently available data, it is unclear if (or to what the extent) this substance may represent any lower risk to workers regarding systemic toxicity and there are limited concerns with regard to its irritancy potential. Indeed, it has been recommended that respirators, gloves and goggles be used when handling the substance (Chemische Werke Lowi, 1978). No epidemiology data are available to directly inform on the effects in humans, particularly workers, of exposure to ethyl centralite.

On the other hand, there is clear evidence to suggest that, particularly with regard to the aquatic environment, ethyl centralite could confer some moderation of risk to the environment if it were to substitute DBP. However, it should be noted that there are no environmental concerns regarding this use of DBP.

The information on the generation of nitrosamines as likely decomposition products (as discussed in relation to methyl centralite), is also applicable for this substance. Indeed, the use of ethyl centralite in nitrocellulose-based explosives has been associated with the formation of carcinogenic N-nitroso-N-alkylanilines (Wilker, Heeb, Vogelsanger, Petržílek, & Skládal, 2007) .

Table 4.22: Hazard comparison of DBP and ethyl centralite

Hazard endpoint	Ethyl centralite	DBP
Human health		
Acute toxicity	Slight (oral)	
Irritancy	Possibly via inhalation	
Sensitisation		
Repeat dose	Uncertain (NOAEL not yet established)	Toxic
STOT	Potential concern for liver, kidney, ovaries and uterus	Liver, kidney, testes
Reproductive toxicity		1B (male fertility)
Developmental toxicity		1B (males)
Carcinogenicity		Data are insufficient to determine the carcinogenic potential. No evidence of carcinogenicity is available. The CSR assumes that the substance is not a carcinogen
Environment		
Aquatic	Toxic (long-lasting effects)	Very toxic
Other		
Other issues	Carcinogenic degradation products	
Note: grey cells indicate areas where no relevant information is available		

4.3.3.3 Safety issues with the manufacture of ethyl centralite

The Confidential Annex explains that the use of the precursors to ethyl centralite by the applicant would raise serious concerns. Based on hazard classifications and in comparison to the precursors to DBP:

- the carbonyl precursor is acutely toxic (inhalation), may cause skin corrosion and is a hazardous pressurised gas incompatible with the current plant; and
- the amine precursor has more severe acute toxicity properties than the current precursor used by the applicant.

The use of precursors to ethyl centralite would be unlikely to result in a lowering of existing hazards at the workplace for DEZA's workers.

Additional confidential information is presented in: AoA Confidential Annex DBP Propellants DEZA.pdf, Section 4.1.2

4.3.4 Economic feasibility

The discussion presented above for methyl centralite would similarly apply here.

DEZA does not and cannot manufacture ethyl centralite as it does not have the technology and expertise for doing so. The substance is foreign to DEZA's product portfolio and capabilities.

The Confidential Annex to this AoA explains that the manufacture of ethyl centralite could not make use of existing facilities at DEZA's DBP plant. An entire plant rebuild would be required

with a cost that could amount to several millions of Euros and would require a timeline sufficiently long to make any thought of starting production completely unrealistic.

Importantly, due to the inherent technical infeasibility of the substance from the perspective of DUs, it is unclear whether any of them would actually use ethyl centralite as a substitute for DBP. Even if ethyl centralite would prove to be technically feasible for the applicant's customers, the volume of current sales of DBP to propellant manufacturers that could be substituted with ethyl centralite would only be very modest, due to (a) the presence of other established suppliers (see Table 4.23) and (b) the overall small tonnage of moderant that is required in the uses of concern.

Overall, if ethyl centralite were to be chosen by DUs as a substitute for DBP in propellant formulations, DEZA would lose its entire sales of DBP in the field, as it would not be able to produce this substance. Information on DEZA's turnover that is associated with sales of DBP to propellant manufacturers is provided in the SEA (Section 2.2.2.1).

This alternative substance cannot be considered economically feasible for the applicant.

Additional confidential information is presented in: AoA Confidential Annex DBP Propellants DEZA.pdf, Section 4.1.3

4.3.5 Availability

4.3.5.1 Current and projected availability

Availability for the applicant

As discussed above, ethyl centralite is manufactured using technology that is alien to DEZA's current portfolio and capabilities. Phenyl ureas are not possible to manufacture at DEZA's DBP plant, as explained in the Confidential Annex to this AoA.

Availability for the downstream users

From the perspective of the DUs, the market availability of ethyl centralite is given in Table 4.23.

Table 4.23: Market availability of ethyl centralite

Alternative	Data availability	Market availability from the perspective of the downstream users
Ethyl centralite	Limited	Generally available. REACH Registered in May 2013; one registrant shown in Dissemination Portal (100-1,000 t/y)

4.3.5.2 Actions required for improving availability

Availability for the applicant

For ethyl centralite to become available to the applicant, a new production line would have to be opened and a new technology introduced.

The Confidential Annex to this AoA explains the challenges that the applicant would face in researching, trialling and starting the production of ethyl centralite at their plant. The conclusion is that the availability of the substance for the applicant is very unlikely to improve in the foreseeable future, without very significant investment, which in light of the size of the affected market, cannot be justified.

Additional confidential information is presented in: AoA Confidential Annex DBP Propellants DEZA.pdf, Section 4.1.4

Availability for the downstream users

Ethyl centralite is already used in nitrocellulose-based propellant formulations and is generally available on the market for use by propellant manufacturers.

4.3.6 Conclusion on suitability and availability of ethyl centralite

4.3.6.1 Technical suitability

The substance is a phenyl urea the manufacture of which is based on precursors and technology completely unknown and wholly incompatible with the applicant's production plant. Ethyl centralite cannot be considered technically feasible from the applicant's perspective.

From the perspective of the DUs, the substance has received mixed reviews by the manufacturers of propellants, as discussed in the Confidential Annex. The companies consulted with believe that ethyl centralite could theoretically be used as a moderant but it is unusable as a plasticiser. Even as a moderant, ethyl centralite is poorer than DBP, although probably superior than methyl centralite. Literature confirms that the substance is generally used as a stabiliser in nitrocellulose-based propellants where any plasticising effect or moderation of the burning rate are added benefits but not the key purpose of ethyl centralite's addition to the mixture.

Moreover, the association of ethyl centralite and other typical stabilisers in nitrocellulose-based propellants with decomposition products that are classified as or are suspected carcinogens casts serious doubts on the technical suitability of the substance, particularly when active efforts have been made to identify alternative, safer stabilisers for nitrocellulose-based propellants.

4.3.6.2 Reduction of overall risk

Tentatively, in a direct comparison to DBP, ethyl centralite would appear to have a more benign hazard profile compared to DBP. However, concerns exist for humans with regard to its hazard potential under conditions of repeated exposure and its respiratory irritation properties. Limited concerns also exist with regard to its aquatic toxicity. In addition, its presence in propellant powders has been associated with the formation of carcinogenic decomposition products.

Overall, the substance does not appear to have been as thoroughly investigated as DBP – particularly with respect to its repeat dose toxicity. Classification and labelling has been notified but it is currently not harmonised. However, as the risks from exposure to DBP from its use in the formulation and subsequent use of propellants are adequately controlled, the use of ethyl centralite would not result in discernible benefits to DUs' workers' health.

From the perspective of the applicant's workers, the precursors to ethyl centralite would appear to have particularly adverse safety and human health hazard profiles and their handling and use would not confer any improvement to the working conditions for the applicant's staff.

4.3.6.3 Economic feasibility

The cost of establishing a production line for ethyl centralite would be extremely high and totally unjustified in light of the presence of established suppliers of the substance and the very modest

sales that DEZA might potentially achieve. The lack of documented technical feasibility of the substance from the perspective of the DUs cannot create optimism that potential sales would allow DEZA to make a profit from a new production line.

4.3.6.4 Availability

From the perspective of the applicant, the substance is not available as its manufacture is based on technology and precursors that are not available to him. Availability is not expected to improve into the future; the quantity of ethyl centralite that would be sold by DEZA is too small to justify the expense of setting up and operating a new production line based on new technology.

On the contrary, for DUs, market availability is believed to be acceptable as the substance already finds applications in propellant formulations.

Key point 11

Ethyl centralite is not a realistic alternative for the applicant and cannot be considered technically or economically feasible. There may also be concerns with regard to its repeat dose toxicity

c) ALTERNATIVE SUBSTANCE: AKARDITE I (1,2-DIPHENYL UREA)

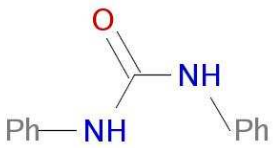
4.4 Akardite I

4.4.1 Substance ID and properties

4.4.1.1 Name and other identifiers for the substance

The following Table presents the identity of Akardite I.

Table 4.24: Identity of Akardite I

Parameter	Value	Source
EC number	203-003-7	1
EC name	1,3-diphenylurea	1
CAS number	102-07-8	1
IUPAC name	1,3-diphenylurea	2
Other names	Akardite I N'N'-diphenyl urea urea, N,N'-diphenyl- 1,3-diphenylcarbamide 1,3-Diphenyl-urea Acardite Carbanilide Diphenyl urea, unsym Diphenylcarbamide S-diphenylurea Sym-diphenylurea Urea, 1,3-diphenyl-	2
Molecular formula	$C_{13}H_{12}N_2O$	1
SMILES notation	c1ccc(cc1)NC(=O)Nc2ccccc2	2
Molecular weight	212.25	2
Molecular structure		1
Sources: *1: ESIS Internet site: http://esis.jrc.ec.europa.eu/* *2: Chemspider Internet site: http://www.chemspider.com/Chemical-Structure.7314.html*		

4.4.1.2 Composition of the substance

No information is currently available. The substance does not appear on ECHA's database of registered substances[23].

4.4.1.3 Physico-chemical properties

The following Table summarises the available information on the physicochemical properties of Akardite I. The information has been collected from a number of literature sources and through consultation with stakeholders.

Table 4.25: Physicochemical properties of Akardite I

Property	Value	Remarks	Source
Physical state at 20°C and 101.3 kPa	Solid		1
Melting/freezing point	238-240°C		1
	189°C	Consultation response	
Boiling point	260-262°C		1
Density	1.239g/cm^3		2
Vapour pressure	1.47 x 10^{-3} kPa at 25°C	ACD/Labs' ACD/PhysChem Suite	1
	1 x 10-6 kPa at 25°C	Expert database	1
	3.33 x 10^{-6} kPa at 25°C		3
Surface tension	56.39 dyne/cm	ACD/Labs' ACD/PhysChem Suite	1
Water solubility	103.7 mg/L at 25°C	LogK$_{ow}$ (WSKOW v1.41) (EPISuite)	1
	150 mg/L at 20°C	Yalkowsky, SH & Dannenfelser, RM (1992) Stephen H & Stephen T (1963) The Merck Index. 9th ed. Rahway, New Jersey: Merck & Co., Inc., 1976., p. 227	1, 4
	1.947 mg/L	Estimate from Fragments	1
Partition coefficient n-octanol/water	2.97	KOWWIN v1.67 estimate (EPISuite)	1
	3.00	Exper. database match	1
Flash point	91.147°C	ACD/Labs' ACD/PhysChem Suite	1
	170.7°C		3
Flammability	No data		
Explosive properties	No data		
Self-ignition temperature	No data		
Oxidising properties	No data		
Granulometry	No data		

Source:
1: Chemspider Internet site: http://www.chemspider.com/Chemical-Structure.7314.html
2: Alfa Aesar Internet site: http://www.alfa.com/en/GP100W.pgm?DSSTK=A18720
3: ChemNet Internet site: http://www.chemnet.com/cas/en/102-07-8/Diphenylcarbamide.html
4: HSDB Internet site: http://toxnet.nlm.nih.gov/cgi-bin/sis/search/f?./temp/~scXmAZ:1

[23] Date of last search: 4 July 2013.

4.4.1.4 Classification and labelling

An online search was performed using the CAS number in ECHA's C&L Inventory. No information on harmonised classification and labelling for Akardite I is available. However, from the ECHA C&L Inventory database two aggregated notifications have been identified. These are presented in Table 4.26.

Table 4.26: Notified classification and labelling of Akardite I according to CLP criteria

Classification		Labelling		Number of Notifiers
Hazard Class and Category Code(s)	**Hazard Statement Code(s)**	**Hazard Statement Code(s)**	**Pictograms Signal Word Code(s)**	
Harmful in contact with skin	H312		GHS07 Wng	2
Harmful if inhaled	H332			
Harmful if swallowed	H302			

4.4.1.5 REACH Registration details

The following Table summarises the available information on the status of REACH Registration of Akardite I.

Table 4.27: REACH Registration status of Akardite I

Registration	Result	Date of last search
Pre-registered	Yes – Envisaged Registration deadline: 30/11/2010	4 June 2012
Registered	No	20 June 2013
Source: *European Chemicals Agency: http://echa.europa.eu/*		

4.4.2 Technical feasibility

4.4.2.1 Technical feasibility from the perspective of the applicant

DEZA does not currently manufacture this substance and does not have any current plans to start production in the future without a clear indication from its DUs that Akardite I would be a technically feasible and acceptable alternative.

The Confidential Annex to this AoA explains that DEZA does not have access to the precursors to Akardite I and their use by the DEZA plant that currently manufactures DBP could potentially be technically infeasible for technical and safety reasons.

Importantly, the manufacture of Akardite I is based on entirely different technology which is not within DEZA's capabilities. DEZA's esterification plant can produce a range of phthalates (depending on the availability of precursor alcohols) and other esters, should the raw materials became available, but does not have the ability to manufacture phenyl ureas. Technically, this alternative cannot be considered feasible for the applicant.

Additional confidential information is presented in: AoA Confidential Annex DBP Propellants DEZA.pdf, Section 4.1.2

4.4.2.2 Technical feasibility from the perspective of downstream users

Relevance as substitute for DBP

According to consultation, the relevance of the substance as a substitute for DBP in propellant mixtures is as follows:

Substance family	Diphenyl ureas
Function	Moderant

Background to the use of the substance

Functions of Akardite I in propellants: literature suggests that Akardite I is a stabiliser for double-base propellants without any pronounced plasticising effect (Meyer, Köhler, & Homburg, 2007).

Non-explosive uses of Akardite I: the substance may be used in organic synthesis[24].

Comparison against key technical feasibility and selection criteria

Trials with the substance and perceived overall technical suitability: this information is presented in the Confidential Annex.

Comparison against the key technical feasibility and selection criteria: this information is presented in the Confidential Annex.

Other technical considerations: the issues associated with the generation of carcinogenic decomposition products when centralites are present in nitrocellulose-based mixtures were discussed earlier. Akardites are urea derivatives therefore decomposition might also result in compounds with carcinogenic potential. However, while centralites form N-nitroso-N-alkylanilines, Akardites form N-nitroso-diphenylamines, which are only suspected to be carcinogenic (Wilker, Heeb, Vogelsanger, Petržílek, & Skládal, 2007).

Whilst Akardites cause lower concern compared to centralites, the generation of decomposition products makes them less than ideal substitutes for DBP in nitrocellulose-based propellants.

Additional confidential information is presented in: AoA Confidential Annex DBP Propellants DEZA.pdf, Section 4.4.3.1

4.4.3 Reduction of overall risk due to transition to the alternative

4.4.3.1 Hazard information

Information on the hazards of Akardite I has been sought from a variety of sources, given that the substance has not been registered in the EU and information from a CSR is not available. Information on the nature of the hazards posed by the substance are summarised in Table 4.28, while the mammalian and ecotoxicological hazardous properties are discussed in more detail below.

[24] Information from the Hazardous Substances Data Bank: http://toxnet.nlm.nih.gov/cgi-bin/sis/search/f?./temp/~scXmAZ:1.

Table 4.28: Hazard information on Akardite I

Database	Parameter	Value
Canada Domestic Substance List (DSL) (2007)	Substance category	Organics
	Bioaccumulative	No (rationale: QSAR)
	Persistent	No (rationale: QSAR)
	Inherently Toxic to Aquatic Organisms	No (rationale: QSAR)
	Meets CEPA Categorization Criteria	No
	Meets Environmental Criteria for Categorization	No
	Meets Human Health Criteria	No
	DSL Quantity range (tonnes/year)	0-1
NLM TOXNET Toxicology	National Technical Information Service. Vol. AD277-689	LD_{50} = 200mg/kg (mouse)
	Journal of Pharmacology and Experimental Therapeutics. Vol. 90, Pg. 260, 1947	LD_{Lo} = 500 mg/kg (rat)
	Szybalski, W; Ann Ny Acad Sci 76: 475 (1958)	Non-mutagenic
Chemical Carcinogenesis Research Information System	Zeiger, E, Anderson, B, Haworth, S, Lawlor, T and Mortelmans, K (1988): *Salmonella Mutagenicity Tests: IV. Results from the Testing of 300 Chemicals*, Environ. Mol. Mutagen., Vol 11(Suppl.12), pp1-158.	Mutagenicity (Ames assay on *S. typhimurium*): negative
Sources: *OECD Internet site: http://webnet.oecd.org/ccrweb/ChemicalDetails.aspx?ChemicalID=6F54EAC3-3A80-4C02-881A-8E78261AB7EC* *US EPA ACToR Internet site: http://actor.epa.gov/actor/GenericChemical?casrn=102-07-8* *Chemical Carcinogenesis Research Information System Internet site: http://toxnet.nlm.nih.gov/cgi-bin/sis/search/r?dbs+ccris%3A%40term+%40rn+102-07-8*		

Additional data, as presented in Table 4.29, on the environmental and ecotoxicological properties of Akardite I are available from the Canada Domestic Substance List referred to above. This can be seen to be largely based on estimates and predictions derived from a number of QSAR systems rather than reports from experimental studies per se.

Table 4.29: Ecological data supporting decisions of Environment Canada on Akardite I

Parameter	Value
Persistence	
Media of concern leading to Categorization	Water
Experimental biodegradation half-life (days)	Not Available
Predicted ultimate degradation half-life (days)	15
Biodegradation (by MITI)	0.0831
Biodegradation (by TOPKAT)	0.826
Ozone reaction half-life (days) (predicted by EPI)	999
Atmospheric oxidation half-life (days) (predicted by EPI)	0.1254
Bioaccumulation potential	
$LogK_{ow}$ (predicted by KowWin)	3
Log BAF T2MTL (predicted by Gobas)	2.97
Log BCF 5% T2LTL (predicted by Gobas)	1.815
Log BCF max (predicted by OASIS)	1.715
Log BCF (predicted by BCFWIN)	1.61

Parameter	Value
Aquatic Toxicity	
Pivotal value for iT (mg/L)	10.5
Acute toxicity to fathead minnow (LC_{50} in mg/L) (predicted by TOPKAT v6.1)	10.5
Acute toxicity to fish (LC_{50} in mg/L) (predicted by Ecosar v0.99g)	19.278
Acute toxicity to fish (LC_{50} in mg/L) (predicted by Oasis Forecast M v1.10)	16.66
Acute toxicity to fish (LC_{50} in mg/L) (predicted by Aster)	18.83
Acute toxicity to fish (LC_{50} in mg/L) (predicted by PNN)	21.62
Acute toxicity to daphnia (EC_{50} in mg/L) (predicted by TOPKAT v6.1)	2.4
Acute toxicity to aquatic organisms(fish, daphnia, algae or mysid shrimp) (EC_{50} or LC_{50} in mg/L) (predicted by Ecosar v0.99g)	0.043
Acute toxicity to fish (LC_{50} in mg/L) (predicted by Neutral Organics QSAR in Ecosar v0.99g)	6.43
Chronic toxicity to daphnia or algae (EC_{50} in mg/L) (predicted by Ecosar v0.99g)	1.732
Source: OECD Internet site: http://webnet.oecd.org/ccrweb/ChemicalDetails.aspx?ChemicalID=6F54EAC3-3A80-4C02-881A-8E78261AB7EC	

QSAR models (OECD QSAR toolbox and FDA EKDB models) were also employed to provide additional insight into the mammalian hazard and ecotoxicological profile of this substance. The outputs of the modelling (and associated references) are presented in Table 4.30. Based on all available information, the hazard profile of this substance may be summarised as follows.

Mammalian hazard profile

Acute toxicity: Akardite I is reported not to meet the Human Health Criteria under the Canada Domestic Substance List, while the available estimated acute toxicity data (LC_{50} values in rodents, assumed to refer to oral route, Table 4.28) suggest that, were it to be classified under CLP, it would be likely to be considered as a Category 3 acute toxin. On the other hand, information noted in Table 4.14 of the Non-confidential document from the ECHA C&L inventory, indicates that Akardite I warrants the H302 (harmful if swallowed) and H332 (harmful if inhaled) precautionary statements with regard to its acute toxic potential.

Repeat dose toxicity: no information is available on the repeat dose toxicity of Akardite I.

Irritancy and sensitisation: as noted in Table 4.15 of the Non-confidential document, the ECHA C&L Inventory identifies two aggregated notifications in which Akardite I is given the H312 (skin toxicity) precautionary statement. QSAR modelling did not however, raise any further concern with regard to its potential irritancy. No information is available on the sensitisation potential of the substance.

Genotoxicity and carcinogenicity: other than one positive QSAR prediction of DNA reactivity that was based on an analysis of Ashby fragments (drawn from the Danish EPA Database), a series of QSAR predictions of in vitro and in vivo mutagenicity and clastogenicity indicate that Akardite I is unlikely to be mutagenic, nor is it of concern with regard to clastogenicity. Similarly, the available QSAR predictions of carcinogenic potential raise little concern.

Reproductive and developmental toxicity: no information or predictions are available with regard to the potential reproductive toxicity of this substance. The OECD QSAR prediction (based on the TERIS database) suggests that it is negative for developmental toxicity.

Table 4.30: Human health and environmental hazard profile for Akardite I

Hazard endpoint		Finding	Data source	Study design	Assessed robustness/Comment
Toxicokinetics		Extent of absorption = 90.2%	OECD QSAR	QSAR prediction of human intestinal absorption by Multicase expert system	Result reported to be undefined with regard to domain applicability, hence considered of uncertain reliability
Irritation	Skin irritation/corrosion	Not Irritating or Corrosive to skin	OECD QSAR	QSAR prediction by Bundesinstitut für Risikobewertung (BfR) skin irritation/corrosion	Result with respect to severe skin irritation reported to be undefined with regard to domain applicability, hence considered of uncertain reliability
		Not Irritating or Corrosive to skin	OECD QSAR	QSAR prediction by BfR skin irritation/corrosion	Result reported to be undefined with regard to domain applicability, hence considered of uncertain reliability
	Eye irritation	Undefined	OECD QSAR	QSAR prediction by BfR eye irritation/corrosion	Result reported to be undefined with regard to domain applicability, hence considered of uncertain reliability
Genetic toxicity	In vitro – Mutagenicity	Negative	Bacterial mutagenicity ISSSTY (in OECD QSAR)	Read-across on Ames Test (*S. typhimurium* Strain TA 100) with S9 activation, from Romualdo Benigni	N/A
		Negative	Bacterial mutagenicity ISSSTY (in OECD QSAR)	Read-across on Ames Test (*S typhimurium* Strain TA 1535) with S9 activation, from Romualdo Benigni	N/A
		Negative	Bacterial mutagenicity ISSSTY (in OECD QSAR)	Read-across on Ames Test (*S typhimurium* Strain TA 97) with S9 activation, from Romualdo Benigni	N/A
		Negative	Bacterial mutagenicity ISSSTY (in OECD QSAR)	Read-across on Ames Test (*S typhimurium* Strain TA 98) with S9 activation, from Romualdo Benigni	N/A
		Negative	Bacterial mutagenicity ISSSTY (in OECD QSAR)	Read-across on Ames Test (*S typhimurium* Strain TA 100) without S9 activation, from Romualdo Benigni	N/A
		Negative	Bacterial mutagenicity ISSSTY (in OECD QSAR)	Read-across on Ames Test(*S. typhimurium* Strain TA 1535) without S9 activation, from Romualdo Benigni	N/A
		Negative	Bacterial mutagenicity ISSSTY (in OECD QSAR)	Read-across on Ames Test (*S. typhimurium* Strain TA 97) without S9 activation, from Romualdo Benigni	N/A
		Negative	Bacterial mutagenicity ISSSTY (in OECD QSAR)	Read-across on Ames Test (*S. typhimurium* Strain TA 98) without S9 activation, from Romualdo Benigni	N/A

Hazard endpoint		Finding	Data source	Study design	Assessed robustness/Comment
		Negative	Genotoxicity OASIS (in OECD QSAR)	Derivation and validation of toxicophores for mutagenicity prediction, based on read-across from Ames Test (on *S. typhimurium*). No information available as to strain(s) or S9 metabolic activation status, from Kazuis *et al*	No reporting of strains addressed or metabolic status precludes meaningful interpretation
		Negative	OECD QSAR	Prediction for mammalian cell unscheduled DNA-damage and repair assay. No definition of species or cell type employed but stated to include rat (S9) metabolic activation, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Positive	OECD QSAR	QSAR prediction for DNA reactivity based on DNA reactivity assay using Ashby fragments, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Negative	OECD QSAR	QSAR prediction for mouse COMET Assay, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
	In vitro – Chromosomal effect	Negative	OECD QSAR	QSAR prediction for mammalian chromosome aberration test, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Negative	OECD QSAR	QSAR prediction for sister chromatid exchange in Syrian Hamster Embryo (SHE) assay, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
	In vivo - Mutagenicity	Negative	OECD QSAR	QSAR prediction for sex-linked recessive lethal assay in *Drosophila melanogaster*, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
	In vivo – Chromosomal effect	Negative	OECD QSAR	QSAR prediction for mouse micronucleus assay, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Negative	OECD QSAR	QSAR prediction for rodent dominant lethal assay, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
Carcinogenicity		Negative	OECD QSAR	QSAR prediction based on FDA Cancer Female Mouse Assay, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Negative	OECD QSAR	QSAR prediction based on FDA Cancer Male Mouse Assay, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable

Hazard endpoint		Finding	Data source	Study design	Assessed robustness/Comment
		Negative	OECD QSAR	QSAR prediction for Mouse Lymphoma, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Carcinogenic potency value (TD_{50}) = 1000 mg/kg	OECD QSAR	QSAR prediction for Mouse Carcinogenic Potency Database (CPDB), from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Negative	OECD QSAR	QSAR prediction based on FDA Cancer Female Rat, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Negative	OECD QSAR	QSAR prediction based on FDA Cancer Male Rat, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Carcinogenic potency value (TD_{50}) = 1000 mg/kg	OECD QSAR	QSAR prediction for Rat Carcinogenic Potency Database (CPDB), from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
Developmental toxicity/ teratogenicity		Negative	OECD QSAR	QSAR prediction based on FDA Teratogen Information System (TERIS), from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable. Prediction supported by lack of reported effects from SHE assay (see above)
Toxicity to reproduction	Reproductive	No information			
Other toxic endpoints	Protein binding potential	No alert found	OECD QSAR	QSAR prediction	No indication identified that model was operating outside of its operational limits
		No alert found	OASIS (in OECD QSAR)	QSAR prediction	No indication identified that model was operating outside of its operational limits
	Androgen receptor binding activity	-2.25 to -1.73 log RBA	FDA EKDB model	Model drew comparison with hydroxylinuron and linuron	Model reports that on basis of only limited similarity with compounds in database (0.46-0.51), no conclusion should be drawn
	Oestrogen gene activation	-10,000 log RP (relative potency)	FDA EKDB model	Model drew comparison with carbendazim, N-Methylaniline and N,N-Dimethylaniline	Model reports that on basis of only limited similarity with compounds in database (0.56-0.60), no conclusion should be drawn
	Oestrogen receptor binding activity	10%	OECD QSAR	QSAR prediction by oestrogen receptor binding activity (Multicase)	Reported to be outside of QSAR domain, hence considered of doubtful reliability

Hazard endpoint		Finding	Data source	Study design	Assessed robustness/Comment
		Negative	OECD QSAR	QSAR prediction by relative oestrogen receptor binding activity, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		-100 to -10,000 log RP	FDA EKDB model	Model drew comparison with 4,4'-Methylenebis(N,N-dimethylaniline), M2 and M1	Model reports that on basis of only limited similarity with compounds in database (0.30-0.37), no conclusion should be drawn
Aquatic toxicity	Fish	5 mg/L (14 hour)	Aquatic US-EPA ECOTOX (in OECD QSAR)	Based on Applegate et al. (1957) 'Toxicity of 4,346 Chemicals to Larval Lampreys and Fishes' reporting of a static test on *Oncorhynchus mykiss* for which multiple effect endpoints combined to give single metric of toxicity	Based on pre-GLP study of unknown design
	Fish	5 mg/L (24 hour)	Aquatic US-EPA ECOTOX (in OECD QSAR)	Based on Applegate et al. (1957) 'Toxicity of 4,346 Chemicals to Larval Lampreys and Fishes' reporting of a static test on *Lepomis macrochirus* for which multiple effect endpoints combined to give single metric of toxicity	Based on pre-GLP study of unknown design
	Fish	5 mg/L (24 hour)	Aquatic US-EPA ECOTOX (in OECD QSAR)	Based on Applegate et al. (1957) 'Toxicity of 4,346 Chemicals to Larval Lampreys and Fishes' reporting of a static test on *Petromyzon marinus* for which multiple effect endpoints combined to give single metric of toxicity	Based on pre-GLP study of unknown design
		LC_{50} = 28.4 mg/L	OECD QSAR	QSAR prediction for lethality in Fathead minnow (*Pimephales promelas*) from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		LC_{50} = 13.4(1.2-149) mg/L	OECD QSAR	QSAR prediction for lethality in Fathead minnow from by M1 - LC_{50} model	Reported to be within QSAR domain, hence considered acceptable
	Not reported	Behavioural effect at 0.118 mg/L	OECD QSAR	QSAR estimation of a behaviour endpoint for an unspecified taxa using uTOX (Multicase)	Reported to be outside of QSAR domain, hence considered of doubtful reliability
	Invertebrate (*assumed*)	Immobilisation EC_{50} = 0.118 mg/L	OECD QSAR	QSAR estimation of immobilisation endpoint for an unspecified taxa using uTOX (Multicase)	Reported to be outside of QSAR domain, hence considered of doubtful reliability

Hazard endpoint		Finding	Data source	Study design	Assessed robustness/Comment
	Not reported	Mortality EC_{50} = 0.118mg/L	OECD QSAR	QSAR estimation of mortality for an unspecified taxa using uTOX (Multicase)	Reported to be outside of QSAR domain, hence considered of doubtful reliability
	Bacteria	EC_{50} = 0.118mg/L	OECD QSAR	QSAR estimation of undefined endpoint by uTOX (Multicase) for a 5 minute lethality in *Vibrio fischeri*	Reported to be outside of QSAR domain, hence considered of doubtful reliability
Terrestrial toxicity	Plant	Survival = 0% (14 days)	Terrestrial US-EPA ECOTOX (in OECD QSAR)	Based on Bruce & Zwar (1966) 'Cytokinin Activity of Some Substituted Ureas and Thioureas' on *Nicotiana tabacum,* measuring population survival	N/A
	Plant	Growth = 1500% (30 days)	Terrestrial US-EPA ECOTOX (in OECD QSAR)	Based on Torigoe et al. (1972) 'Cytokinin Activity of Azaindene, Azanaphthalene, Naphthalene, and Indole Derivatives' using an in vitro tobacco (*Nicotiana tabacum)* pith callus bioassay to assessing growth based on biomass	Relevance and predictivity of underling assay system to prediction of in vivo behaviour uncertain
	Plant	Growth = 240% (30 days)	Terrestrial US-EPA ECOTOX (in OECD QSAR)	Based on Torigoe et al. (1972) 'Cytokinin Activity of Azaindene, Azanaphthalene, Naphthalene, and Indole Derivatives' using an in vitro tobacco (*Nicotiana tabacum)* pith callus bioassay to assessing growth based on biomass	Relevance and predictivity of underling assay system to prediction of in vivo behaviour uncertain
	Plant	Growth = 1770% (30 days)	Terrestrial US-EPA ECOTOX (in OECD QSAR)	Based on Torigoe et al. (1972) 'Cytokinin Activity of Azaindene, Azanaphthalene, Naphthalene, and Indole Derivatives' using an in vitro tobacco (*Nicotiana tabacum)* pith callus bioassay to assessing growth based on biomass	Relevance and predictivity of underling assay system to prediction of in vivo behaviour uncertain

Sources:
OECD QSAR Data obtained using OECD QSAR Toolbox at Internet site:
http://www.oecd.org/chemicalsafety/assessmentofchemicals/theoecdqsartoolbox.htm#Download_qsar_application_toolbox
FDA EKDB data obtained using FDA EKDB Database at Internet site:
http://www.fda.gov/ScienceResearch/BioinformaticsTools/EndocrineDisruptorKnowledgebase/default.htm

Other toxicities: QSAR modelling using the OECD toolbox to inform on the substance's ability to interact with proteins identified no concerns, though the model was reported as operating outside of its domain and, hence, this cannot be considered as a reliable prediction. Similarly, although again identifying no alerts, the predictions on androgenic and oestrogenic receptor and gene activation potential generated by the FDA EKDB model appear unreliable. However, a QSAR prediction of a negative response for relative oestrogen receptor binding activity from the Danish EPA Database, appears robust.

Environmental fate and behaviour and ecotoxicology

Available information in Table 4.30, based largely on the outputs of various QSAR models, does not raise concern for either the persistence or bioaccumulative potential of the substance in the environment. No published experimental aquatic toxicity data were identified, but QSAR predictions of the toxicity of Akardite I to aquatic organisms suggest that it is not acutely toxic to fish but may pose some measure of acute risk to invertebrates and bacteria. However, it appears unlikely that it would warrant classification as a chronic environmental toxin.

QSAR predictions of toxicity to terrestrial organisms, based on an in vitro tobacco (*Nicotiana tabacum*) pith callus bioassay for plant growth generally also do not raise concerns with regard to the toxicity of the substance in this taxa. These findings – supported by the conclusions of the Canadian Authorities – suggest that there is unlikely to be significant concern for the aquatic or terrestrial toxicity of Akardite I.

4.4.3.2 Comparison of hazards

The following Table compares the limited information (mainly from QSAR models) available on the hazard profile of Akardite I to that established for DBP. Whilst there is an extensive dataset to draw upon in the case of DBP, it should be stressed that the assessment of Akardite I involves a considerable measure of uncertainty given the extensive reliance on QSAR predictions of varying robustness and, importantly, the gap in understanding of its toxic profile in relation to repeat dose toxicity and reproductive toxicity.

Nonetheless, available data suggest that Akardite I may show a degree of acute toxicity (which could have limited implications for the acute risks faced by workers). Its repeat dose and reproductive toxicity are unknown (though a limited measure of reassurance for the latter may be derived from a lack of QSAR alerts in respect of its interaction with endocrine receptors). However, it appears that it is unlikely to constitute the same level of environmental hazard as DBP.

Table 4.31: Hazard comparison of DBP and Akardite I

Hazard endpoint	Akardite I	DBP
Human health		
Acute toxicity	Slight/moderate (oral, inhalation)	
Irritancy	Skin (?)	
Sensitisation		
Repeat dose		Toxic
STOT		Liver, kidney, testes
Reproductive toxicity		1B (male fertility)
Developmental toxicity		1B (males)

Hazard endpoint	Akardite I	DBP
Carcinogenicity		Data are insufficient to determine the carcinogenic potential. No evidence of carcinogenicity is available. The CSR assumes that the substance is not a carcinogen
Environment		
Aquatic		Very toxic
Other		
Other issues	Potential for carcinogenic degradation products	
Note: grey cells indicate areas where no relevant information is available		

It should be noted, however, that the presence of Akardites in nitrocellulose-based propellants may be associated with the formation of potentially carcinogenic N-nitroso compounds. Their potency would be considered lower than that of the decomposition compounds linked to centralites, but they have not been investigated as thoroughly.

4.4.3.3 Safety issues with the manufacture of Akardite I

The Confidential Annex explains that the use of the precursors to Akardite I by the applicant would raise serious concerns. Based on hazard classifications and in comparison to the precursors to DBP:

- the carbonyl precursor is flammable, acutely toxic (by inhalation), may cause skin corrosion and highly toxic to the aquatic environment (acute and chronic); and
- the amine precursor has more severe acute toxicity properties than the current precursor used by the applicant, it is a skin sensitiser, causes damage to the eyes, has mild mutagenic and carcinogenic properties and is highly toxic to the aquatic environment (acute).

The use of precursors to Akardite I would be unlikely to result in a lowering of existing hazards at the workplace for DEZA's workers.

Additional confidential information is presented in: AoA Confidential Annex DBP Propellants DEZA.pdf, Section 4.1.2

4.4.4 Economic feasibility

The discussion presented above for methyl and ethyl centralites would similarly apply here.

DEZA does not and cannot manufacture Akardite I, as it does not have the technology and expertise for doing so. The substance is foreign to DEZA's product portfolio and capabilities.

The Confidential Annex to this AoA explains that the manufacture of Akardite I could not make use of existing facilities at DEZA's DBP plant. An entire plant rebuild would be required with a cost that could amount to several millions of Euros and would require a timeline sufficiently long to make any thought of starting production completely unrealistic.

Importantly, due to the inherent technical infeasibility of the substance from the perspective of DUs, it is unclear whether any of them would actually use Akardite I as a substitute of DBP. Even if Akardite I would prove to be technically feasible for the applicant's customers, the volume of current sales of DBP to propellant manufacturers that could be substituted with Akardite I would

only be very modest, due to the overall small tonnage of moderant that is required in the "Applied for" Use.

Overall, if Akardite I were to be chosen by DUs as a substitute for DBP in propellant formulations, DEZA would lose its entire sales of DBP in the field, as it would not be able to produce this substance. Information on DEZA's turnover that is associated with sales of DBP to propellant manufacturers is provided in the SEA (Section 2.2.2.1).

This alternative substance cannot be considered economically feasible for the applicant.

Additional confidential information is presented in: AoA Confidential Annex DBP Propellants DEZA.pdf, Section 4.1.3

4.4.5 Availability

4.4.5.1 Current and projected availability

Availability for the applicant

As discussed above, Akardite I is manufactured using technology that is alien to DEZA's current portfolio and capabilities. Phenyl ureas are not possible to manufacture at DEZA's DBP plant, as explained in the Confidential Annex to this AoA.

Availability for the downstream users

From the perspective of the DUs, the market availability of Akardite I is given in Table 4.32.

Table 4.32: Market availability of Akardite I

Alternative	Data availability	Market availability from the perspective of the downstream users
Akardite I	Very limited	Potentially available. Some consultees have experienced difficulty in sourcing the substance Not REACH registered

4.4.5.2 Actions required for improving availability

Availability for the applicant

For Akardite I to become available to the applicant a new production line would have to be opened and a new technology introduced.

The Confidential Annex to this AoA explains the challenges that the applicant would face in researching, trialling and starting the production of Akardite I at their plant. The conclusion is that the availability of the substance for the applicant is very unlikely to improve in the foreseeable future, without very significant investment, which in light of the size of the affected market, cannot be justified.

Additional confidential information is presented in: AoA Confidential Annex DBP Propellants DEZA.pdf, Section 4.1.4

Availability for the downstream users

No specific information is available.

4.4.6 Conclusion on suitability and availability of Akardite I

4.4.6.1 Technical suitability

The substance is a phenyl urea the manufacture of which is based on precursors and technology completely unknown and wholly incompatible with the applicant's production plant. Akardite I cannot be considered technically feasible from the applicant's perspective.

From the perspective of the DUs, the substance has been described as a potential substitute moderant, but a poor plasticiser. This assessment is only based on informed assumptions and speculation rather than the results of actual testing. As a result, a meaningful comparison to DBP cannot be performed based on existing information. The issue of potentially carcinogenic N-nitroso decomposition products also casts a shadow on the technical feasibility of the substance, although Akardites cause less concern compared to centralites.

4.4.6.2 Reduction in overall risk

Generally, the amount of information available is very limited (particularly in relation to repeat dose toxicity and reproductive toxicity), certainly much more limited compared to the DBP dataset. There are indications of some acute toxicity and the known issue of the generation of potentially carcinogenic N-nitroso decomposition products, although such issues may be less prominent in comparison to centralites. Nevertheless, as the risks from exposure to DBP from its use in the formulation and subsequent use of propellants are adequately controlled, the use of Akardite I would not result in discernible benefits to DUs' workers' health.

From the perspective of the applicant's workers, the precursors to Akardite I would appear to have unfavourable safety and human health hazard profiles and their handling and use would not confer any improvement to the working conditions for the applicant's staff.

4.4.6.3 Economic feasibility

The cost of establishing a production line for Akardite I would be extremely high and totally unjustified in light of the very modest sales that DEZA might potentially achieve in the field of propellants. The lack of documented technical feasibility of the substance from the perspective of the DUs, cannot create optimism that potential sales would allow DEZA to make a profit from a new production line.

4.4.6.4 Availability

From the perspective of the applicant, the substance is not available as its manufacture is based on technology and precursors which are not available to him. Availability is not expected to improve into the future; the quantity of Akardite I that would be sold by DEZA is too small to justify the expense of setting up and operating a new production line based on new technology.

From the perspective of the DUs, some concerns have been expressed as to the ease of obtaining the substance on the market.

Key point 12

Akardite I is not a realistic alternative for the applicant. Its technical feasibility for DUs is uncertain and its economic feasibility is poor. Its hazard profile is largely unknown

d) ALTERNATIVE SUBSTANCE: AKARDITE II (3-METHYL-1,1,-DIPHENYLUREA)

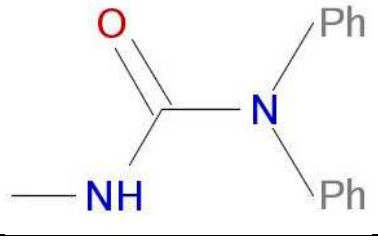
4.5 Akardite II

4.5.1 Substance ID and properties

4.5.1.1 Name and other identifiers for the substance

The following Table presents the identity of the Akardite II.

Table 4.33: Identity of Akardite II

Parameter	Value	Source
EC number	236-039-7	1
EC name	3-methyl-1,1-diphenylurea	1
CAS number	13114-72-2	1
IUPAC name	1,3-diethyl-1,3-diphenylurea	2
Other names	Urea, N'-methyl-N,N-diphenyl- (methylamino)-N,N-dibenzamide 1-Methyl-3,3-diphenylurea N,N-diphenyl-N'-methylurea N'-methyl-N,N-diphenylurea N,N'-diethylcarbanilide Carbamite N,N'-diethyl-N,N'-diphenylurea S-Diethyldiphenylurea Sym-diethyldiphenylurea N,N-Diethylcarbanilide Bis(N-ethyl-N-phenyl)urea Urea, N,N'-diethyl-N,N'-diphenyl- Carbanilide, N'-diethyl-	2, 3
Molecular formula	$C_{14}H_{14}N_2O$	1
SMILES notation	O=C(N(c1ccccc1)c2ccccc2)NC	3
Molecular weight	226.27	2
Structure		1

Sources:
1: ESIS Internet site: http://esis.jrc.ec.europa.eu/
2: PubChem Compound Internet site:
http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=6828&loc=ec_rcs#x27
3: ChemSpider Internet site: http://www.chemspider.com/Chemical-Structure.23952.html

4.5.1.2 Composition of the substance

No information is available on constituents and impurities. The substance does not appear on ECHA's database of registered substances[25].

4.5.1.3 Physico-chemical properties

The following Table summarises the available information on the physicochemical properties of Akardite II. The information has been collected from several literature sources and through consultation with stakeholders.

Table 4.34: Physicochemical properties of Akardite II

Property	Value	Remarks	Source
Physical state at 20°C and 101.3 kPa	Solid	White to light grey crystalline powder Safety Data Sheet provided by consultee	
Melting/freezing point	141.26°C	Mean or Weighted MP (EPI Suite)	1
	170-171.5°C	Safety Data Sheet provided by consultee	
	189°C or 171.2°C or 190°C	Consultation response	
Boiling point	412.913°C at 101.3 mmHg	Predicted data ACD/Labs' ACD/ PhysChem suite	1
	389.02°C	Adapted Stein & Brown method (EPI Suite)	1
Density	1.152 g/cm^3	Predicted data ACD/Labs' ACD/ PhysChem suite.	1
Vapour pressure	0 kPa at 25°C	Predicted data ACD/Labs' ACD/ PhysChem suite.	1
	0.137 x10^{-6} kPa at 25°C	Modified Grain method (EPI Suite)	1
Surface tension	47.805 dyne/cm	Predicted data ACD/Labs' ACD/ PhysChem suite	1
Water solubility	692.6 mg/L at 25°C	Estimate from LogK$_{ow}$ (WSKOW v1.41) - logK$_{ow}$ used: 1.95 (estimated) (EPI Suite)	1
	282.75 mg/L	Estimate from Fragments - Wat Sol (v1.01 est) (EPI Suite)	1
	Insoluble/low solubility	Literature suggests that Akardite II is insoluble in water or very little soluble in water	2, 3
Partition coefficient n-octanol/water	1.95	(Log Octanol-Water Partition Coef (SRC) - LogK$_{ow}$ (KOWWIN v1.67 estimate)) (EPI Suite	1
Flash point	203.523°C	Predicted data ACD/Labs' ACD/ PhysChem suite	1
Flammability	No data		
Explosive properties	No data		
Self-ignition temperature	No data		
Oxidising properties	No data		
Granulometry	No data		
Source: *1: ChemSpider Internet site:* *http://www.chemspider.com/Chemical-Structure.23952.html?rid=f76b4315-f254-4562-9481-57a6a85c0ac1* *2:* (Chemicalland 21, undated) *3:* (Walsh & al, 2010)			

[25] Date of last search: 4 July 2013.

4.5.1.4 Classification and Labelling

No harmonised classification and labelling for Akardite II is available. However, in the ECHA C&L Inventory database one aggregated notification has been identified. This is presented in Table 4.35. Furthermore, the database also suggests that an additional four notifiers have not classified the substance.

Table 4.35: Notified classification and labelling of Akardite II according to CLP criteria

Classification		Labelling		Number of Notifiers
Hazard Class and Category Code(s)	**Hazard Statement Code(s)**	**Hazard Statement Code(s)**	**Pictograms Signal Word Code(s)**	
Eye Irrit. 2	H319	H319 (Eye irritation)	GHS07 Wng	23
Source: *European Chemicals Agency: http://echa.europa.eu/*				

4.5.1.5 REACH Registration details

The following Table shows the status of REACH Registration of Akardite II.

Table 4.36: REACH Registration status of Akardite II

Registration	Result	Date of last search
Pre-registered	Yes – Envisaged Registration deadline: 30/11/2010	4 June 2012
Registered	No	20 June 2013
Source: *European Chemicals Agency: http://echa.europa.eu/*		

4.5.2 Technical feasibility

4.5.2.1 Technical feasibility from the perspective of the applicant

DEZA does not currently manufacture this substance and does not have any current plans to start production in the future without a clear indication from its DUs that Akardite II would be a technically feasible and acceptable alternative.

The Confidential Annex to this AoA explains that DEZA does not have access to the precursors to Akardite II and it is unclear whether these can be easily obtained and how they could be used within DEZA's plant.

Importantly, the manufacture of Akardite II is based on entirely different technology, which is not within DEZA's capabilities. DEZA's esterification plant can produce a range of phthalates (depending on the availability of precursor alcohols) and other esters, should the raw materials became available, but does not have the ability to manufacture phenyl ureas. Technically, this alternative cannot be considered feasible for the applicant.

Additional confidential information is presented in: AoA Confidential Annex DBP Propellants DEZA.pdf, Section 4.1.2

4.5.2.2 Technical feasibility from the perspective of downstream users

Relevance as substitute for DBP

According to consultation, the relevance of the substance as a substitute for DBP in propellant mixtures is as follows:

Substance family	Alkyl diphenyl ureas
Function	Moderant (consultation also suggests a particular relevance as a coolant too)

Background to the use of the substance

Functions of Akardite II in propellants: literature suggests that Akardite II is a component of propellants and it is used as a stabiliser, plasticiser and surface moderant. As discussed earlier in this document, Akardite II has been described as a stabiliser with a plasticising effect (Akardite II is considered one of the best stabilisers for nitrocellulose or energetic plasticiser systems).

Akardite II is often used in propellants containing diethyleneglycol dinitrate (DEGN) (US Army, 1989).

Non-explosive uses of Akardite II: none identified.

Comparison against key technical feasibility and selection criteria

Trials with the substance and perceived overall technical suitability: this information is presented in the Confidential Annex.

Comparison against the key technical feasibility and selection criteria: this information is presented in the Confidential Annex.

Other technical considerations: Akardite II is known to form carcinogens when it reacts with the nitrous oxides formed in the decomposition of the propellant matrix (Langlet, 2006). We discussed earlier the issues associated with the generation of carcinogenic decomposition products when centralites are used. Akardites are urea derivatives therefore decomposition might also result in compounds with carcinogenic potential. However, while centralites form N-nitroso-N-alkylanilines, Akardites form N-nitroso-diphenylamines which are only suspected to be carcinogenic (Wilker, Heeb, Vogelsanger, Petržílek, & Skládal, 2007).

Whilst Akardites cause lower concern compared to centralites, the generation of decomposition products makes them less than ideal substitutes for DBP in nitrocellulose-based propellants.

Additional confidential information is presented in: AoA Confidential Annex DBP Propellants DEZA.pdf, Section 4.5.2.2

4.5.3 Reduction of overall risk due to transition to the alternative

4.5.3.1 Hazard information

Despite extensive searches in several databases and online sources, very little published information has been identified for Akardite II. Given the limited dataset on the hazardous properties of Akardite II that are published, QSAR models (OECD QSAR toolbox and FDA EKDB model) were, therefore, employed to derive additional insight into both the mammalian and ecotoxicological

profile of this substance. The outputs of the modelling (and associated references) are presented in Table 4.37, overleaf.

Based on all available information, the hazard profile of this substance may be summarised as follows.

Mammalian hazard profile

Acute toxicity: available data suggest a low acute toxicity (Oral LD_{50} = 2000 mg/kg bw for mice) for Akardite II (Nippon Kayaku, 2008). This implies that, were these data to be considered in the classification of the substance under CLP, it would be likely to be considered as a Category 4 acute toxin.

Repeat dose toxicity: no information is available on the repeat dose toxicity of Akardite II.

Irritancy and sensitisation: QSAR modelling did not raise concerns with regard to the substance's skin irritancy. However, as noted in Table 4.20 of the Non-confidential document, the ECHA C&L Inventory identifies 23 aggregated notifications in which Akardite II is indicated to warrant a H319 for eye irritation statement. No information is available on its sensitisation potential.

Genotoxicity and carcinogenicity: a series of Ames assays on *S. typhimurium* strains TA97, 98, 100 and 1535, in the presence or absence of metabolic activation, were negative (Zeiger, Anderson, Haworth, Lawlor, & Mortelmans, 1992), while additional QSAR modelling provides further confidence that Akardite II is not mutagenic in prokaryotic organisms irrespective of metabolic status. A QSAR prediction for mutagenicity in *D. melanogaster* was also negative. However, QSAR predictions for unscheduled DNA repair activity in a mouse bone marrow sister chromatid exchange assay and for a mouse micronucleus test gave equivocal and positive responses respectively, raising a limited degree of concern with regard to the potential for genotoxicity to occur in mammalian species in vivo. Several QSAR estimations of rodent carcinogenic potency suggest only low concern is warranted with regard to the substance's carcinogenic potential.

Reproductive and developmental toxicity: no information is available on the potential reproductive toxicity of this substance. The OECD QSAR prediction (based on the TERIS database) indicates that it is not a developmental toxin.

Other toxicities: although not considered to generally provide robust predictions, the QSAR modelling of the substance's ability to interact with proteins or with the oestrogen or androgen receptor did not identify potential concerns with regard to its endocrine disruptive potential. In particular though, the only OECD model output on oestrogen receptor binding affinity that was reported to be within its domain, was negative.

Table 4.37: Human health and environmental hazard profile for Akardite II

Hazard endpoint		Finding	Data source	Study design	Assessed robustness/Comment
Toxicokinetics		96.2%	OECD QSAR	QSAR prediction of human intestinal absorption by Multicase expert system	Result reported to be undefined with regard to domain applicability; hence considered of uncertain reliability
Irritation	Skin irritation/corrosion	Not corrosive to skin	OECD QSAR	QSAR prediction by Bundesinstitut für Risikobewertung (BfR) skin irritation/corrosion	Result undefined with regard to domain applicability; hence considered of uncertain reliability
		Negative	OECD QSAR	QSAR prediction for severe skin irritation, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Not corrosive to skin	OECD QSAR	QSAR prediction by BfR skin irritation/corrosion	Result undefined with regard to domain applicability; hence considered of uncertain reliability
	Eye irritation	Undefined	OECD QSAR	QSAR prediction by BfR eye irritation/corrosion	Result undefined with regard to domain applicability; hence considered of uncertain reliability
Genetic toxicity	In vitro - Mutagenicity	Negative	Genotoxicity OASIS (in OECD QSAR)	Based on Ames Test (*S. typhimurium*, Strain TA 97) without S9 activation, from P&G	N/A
		Negative	Genotoxicity OASIS (in OECD QSAR)	Based on Ames Test (*S. typhimurium*, Strain TA 98) without S9 activation, from P&G	N/A
		Negative	Genotoxicity OASIS (in OECD QSAR)	Based on Ames Test (*S. typhimurium*, Strain TA 100) without S9 activation, from P&G	N/A
		Negative	Genotoxicity OASIS (in OECD QSAR)	Based on Ames Test (*S. typhimurium*, Strain TA 1535) without S9 activation, from P&G	N/A
		Negative	Genotoxicity OASIS (in OECD QSAR)	Based on Ames Test (*S. typhimurium*, Strain TA 1537) without S9 activation, from P&G	N/A
		Negative	Genotoxicity OASIS (in OECD QSAR)	Based on Ames Test (*S. typhimurium*, Strain TA 1538) without S9 activation, from P&G	N/A
		Negative	Genotoxicity OASIS (in OECD QSAR)	Based on Ames Test (*S. typhimurium*, Strain TA 97) with S9 activation, from P&G	N/A

Hazard endpoint		Finding	Data source	Study design	Assessed robustness/Comment
		Negative	Genotoxicity OASIS (in OECD QSAR)	Based on Ames Test (*S. typhimurium*, Strain TA 98) with S9 activation, from P&G	N/A
		Negative	Genotoxicity OASIS (in OECD QSAR)	Based on Ames Test (*S. typhimurium*, Strain TA 100) with S9 activation, from P&G	N/A
		Negative	Genotoxicity OASIS (in OECD QSAR)	Based on Ames Test (*S. typhimurium*, Strain TA 1535) with S9 activation, from P&G	N/A
		Negative	Genotoxicity OASIS (in OECD QSAR)	Based on Ames Test (*S. typhimurium*, Strain TA 1537) with S9 activation, from P&G	N/A
		Negative	Genotoxicity OASIS (in OECD QSAR)	Based on Ames Test (*S. typhimurium*, Strain TA 1538) with S9 activation, from P&G	N/A
		Negative	Genotoxicity OASIS (in OECD QSAR)	Based on Ames Test (*S. typhimurium*) (no strain or S9 information), from Kazius et al	N/A
		Negative	OECD QSAR	QSAR prediction by DNA reactivity, based on DNA reactivity assay using Ashby fragments, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Negative	OECD QSAR	QSAR prediction by Ames test (*S. typhimurium*), from Danish EPA database	Reported to be within QSAR domain, hence considered acceptable
	In vitro – Chromosomal effect	Negative	OECD QSAR	Prediction for mouse bone marrow sister chromatid exchange assay (Hypoxanthine-Guanine Phosphoribosyl Transferase), from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Negative	OECD QSAR	QSAR prediction for sister chromatid exchange in Syrian Hamster Embryo (SHE) assay, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
	In vivo - Mutagenicity	Negative	OECD QSAR	QSAR prediction for sex-linked recessive lethal assay in *Drosophila melanogaster*, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable

Hazard endpoint		Finding	Data source	Study design	Assessed robustness/Comment
		Equivocal	OECD QSAR	QSAR prediction for unscheduled DNA repair response based on a mouse bone marrow sister chromatid exchange assay, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
	In vivo – Chromosomal effect	Positive	OECD QSAR	QSAR prediction for mouse micronucleus assay, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
Carcinogenicity		Negative	OECD QSAR	QSAR prediction based on FDA Cancer Female Mouse, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Negative	OECD QSAR	QSAR prediction based on FDA Cancer Male Mouse, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Negative	OECD QSAR	QSAR prediction for Mouse Lymphoma, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Carcinogenic potency value (TD_{50}) = 1000 mg/kg	OECD QSAR	QSAR prediction for Mouse Carcinogenic Potency Database (CPDB), from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Negative	OECD QSAR	QSAR prediction based on FDA Cancer Female Rat, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Negative	OECD QSAR	QSAR prediction based on FDA Cancer Male Rat, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Carcinogenic potency value (TD_{50}) = 1000 mg/kg	OECD QSAR	QSAR prediction for Rat Carcinogenic Potency Database (CPDB), from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
Toxicity to reproduction		No information			
Developmental toxicity		Negative for teratogenicity	OECD QSAR	QSAR prediction based on FDA Teratogen Information System (TERIS), from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
Other toxic endpoints	Protein binding potential	No alert found	OECD QSAR	QSAR prediction	No indication identified that model was operating outside of its operational limits

Hazard endpoint		Finding	Data source	Study design	Assessed robustness/Comment
		No alert found	OASIS (in OECD QSAR)	QSAR prediction	No indication identified that model was operating outside of its operational limits
	Androgen receptor binding activity	-2.25 to -1.73 log RBA	FDA EKDB model	Model drew comparison with linuron and hydroxy linuron	Model reports that on basis of only limited similarity with compounds in database (0.48-0.44), no conclusion should be drawn
	Oestrogen gene activation	-10,000 log RP (relative potency)	FDA EKDB model	Model drew comparison with diphenylamine, N-phenyl-1-naphthylamine and N-phenyl-2-naphthylamine	Model reports that on basis of only limited similarity with compounds in database (0.61-0.63), no conclusion should be drawn
	Oestrogen receptor binding activity	10%	OECD QSAR	QSAR prediction by oestrogen receptor binding activity (RBA Multicase)	Reported to be outside of QSAR domain, hence considered of doubtful reliability
		Negative	OECD QSAR	QSAR prediction by relative oestrogen receptor binding activity, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		-10000 log RP (relative potency)	FDA EKDB model	Model drew comparison with diphenylamine, n-phenyl-1-naphthylamine and n-phenyl-2-naphthylamine	Model reports that on basis of only limited similarity with compounds in database (0.61-0.63), no conclusion should be drawn
Aquatic toxicity	Taxa not specified	0.016 mg/L	OECD QSAR	QSAR estimation of behaviour endpoint by uTOX (Multicase)	Reported to be within QSAR domain, hence considered acceptable
	Taxa not specified	Immobilisation EC_{50} = 0.016 mg/L	OECD QSAR	QSAR estimation of immobilisation endpoint by uTOX (Multicase)	Reported to be within QSAR domain, hence considered acceptable
	Invertebrate	Immobilisation EC_{50} = 0.51 mg/L (48 hour)	OECD QSAR	QSAR estimation by EC50 for *D. magna*, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
	Taxa not specified	0.016 mg/L	OECD QSAR	QSAR estimation of undefined endpoint by uTOX (Multicase)	Reported to be within QSAR domain, hence considered acceptable
	Bacteria	EC_{50} = 0.016 mg/L	OECD QSAR	QSAR estimation of undefined endpoint by uTOX (Multicase) for a 5 minute lethality in *Vibrio fischeri*	Reported to be within QSAR domain, hence considered acceptable

Sources:
OECD QSAR Data obtained using OECD QSAR Toolbox at Internet site:
http://www.oecd.org/chemicalsafety/assessmentofchemicals/theoecdqsartoolbox.htm#Download_qsar_application_toolbox
FDA EKDB data obtained using FDA EKDB Database at Internet site:
http://www.fda.gov/ScienceResearch/BioinformaticsTools/EndocrineDisruptorKnowledgebase/default.htm

Environmental fate and behaviour and ecotoxicology

Available information, based largely on the outputs of various QSAR models, does not raise concern for either the persistence or bioaccumulative potential of the substance in the environment.

No published experimental ecotoxicity data were identified in the searches conducted for this exercise, and no classification for ecotoxicity has been included in the ECHA C&L Inventory, though this is noted to be due to the lack of data. When limited QSAR modelling of the ecotoxic profile of Akardite II were undertaken, findings for aquatic taxa raised a possible concern with regard to its acute aquatic toxicity, with an EC_{50} value for immobilisation in daphnids of only 0.51 mg/L predicted for a 48-hour test. This would be a level indicative of an acute toxicity Category 1 assignment were these QSAR-generated data to be used for classification under CLP.

No information is available on the toxicity to terrestrial species and the QSAR output available, though of limited nature, does not provide convincing evidence that there should be significant concern with regard to the chronic ecotoxic potential of Akardite II.

4.5.3.2 Comparison of hazards

The following Table compares the available information on the hazard profile of Akardite II to that of DBP. As for Akardite I, the hazard profile of Akardite II established here is subject to a considerable measure of uncertainty, given the extensive reliance on QSAR predictions of varying robustness and, importantly, the gap in understanding of its toxic profile in relation to the important endpoints of repeat dose toxicity and reproductive toxicity.

Table 4.38: Hazard comparison of DBP and Akardite II

Hazard endpoint	Akardite II	DBP
Human health		
Acute toxicity	Slight	
Irritancy	Ocular	
Sensitisation		
Repeat dose		Toxic
STOT		Liver, kidney, testes
Reproductive toxicity		1B (male fertility)
Developmental toxicity		1B (males)
Genotoxicity	Indications from QSAR modelling	
Carcinogenicity		Data are insufficient to determine the carcinogenic potential. No evidence of carcinogenicity is available. The CSR assumes that the substance is not a carcinogen
Environment		
Aquatic	Potentially toxic	Very toxic
Other		
Other issues	Potential for carcinogenic degradation products	
Note: grey cells indicate areas where no relevant information is available		

The Table indicates that, while in several respects Akardite II appears to show a more benign mammalian toxicity and to have a less hazardous ecotoxicological profile than DBP, it is classified as an eye irritant (thereby posing a potential occupational hazard) and there is also reason for limited concern with regard to its potential mammalian genotoxicity. Overall, though, based on limited information, it appears that the use of Akardite II could theoretically reduce hazards to workers and the environment if it substituted DBP. However, this conclusion does not include consideration of the issue of its potential carcinogenic decomposition products. As discussed earlier with respect to Akardite I, Akardites may form decomposition products that are suspected carcinogens. However, in recent research Akardite II has been presented as the least critical stabiliser currently in use. Akardite II is as pure substance markedly less toxic than most of the other stabilisers and produces much smaller amounts of N-nitroso-diphenylamine compared to other stabilisers such as diphenylamine (Wilker, Heeb, Vogelsanger, Petržílek, & Skládal, 2007).

4.5.3.3 Safety issues with the manufacture of Akardite II

The Confidential Annex explains that the use of the precursors to Akardite II by the applicant would raise concerns. Based on hazard classifications and in comparison to the precursors to DBP:

- the carbonyl precursor is flammable, acutely toxic (by inhalation), and mildly reprotoxic; and
- the amine precursor is a skin and eye irritant.

The use of precursors to Akardite II would be unlikely to result in a lowering of existing hazards at the workplace for DEZA's workers.

Additional confidential information is presented in: AoA Confidential Annex DBP Propellants DEZA.pdf, Section 4.1.2

4.5.4 Economic feasibility

The discussion presented above for the other urea derivatives would similarly apply here.

DEZA does not and cannot manufacture Akardite II as it does not have the technology and expertise for doing so. The substance is foreign to DEZA's product portfolio and capabilities.

The Confidential Annex to this AoA explains that the manufacture of Akardite II could not make use of existing facilities at DEZA's DBP plant. An entire plant rebuild would be required with a cost that could amount to several millions of Euros and would require a timeline sufficiently long to make any thought of starting production completely unrealistic.

Importantly, due to the inherent technical infeasibility of the substance from the perspective of DUs, it is unclear whether any of them would actually use Akardite II as a substitute of DBP. Even if Akardite II would prove to be technically feasible for the applicant's customers, the volume of current sales of DBP to propellant manufacturers that could be substituted with Akardite II would only be very modest, due to (a) the presence of other established suppliers (see Table 4.39) and (b) the overall small tonnage of moderant that is required in the "Applied for" Use.

Overall, if Akardite II were to be chosen by DUs as a substitute for DBP in propellant formulations, DEZA would lose its entire sales of DBP in the field, as it would not be able to produce this substance. Information on DEZA's turnover that is associated with sales of DBP to propellant manufacturers is provided in the SEA (Section 2.2.2.1).

This alternative substance cannot be considered economically feasible for the applicant.

Additional confidential information is presented in: AoA Confidential Annex DBP Propellants DEZA.pdf, Section 4.1.3

4.5.5 Availability

4.5.5.1 Current and projected availability

Availability for the applicant

As discussed above, Akardite II is manufactured using technology that is alien to DEZA's current portfolio and capabilities. Phenyl ureas are not possible to manufacture at DEZA's DBP plant, as explained in the Confidential Annex to this AoA.

Availability for the downstream users

From the perspective of the DUs, the market availability of Akardite II is given in Table 4.39.

Table 4.39: Market availability of Akardite II

Alternative	Data availability	Market availability from the perspective of the downstream users
Akardite II	Very limited	Generally available Not REACH registered

4.5.5.2 Actions required for improving availability

Availability for the applicant

For Akardite II to become available to the applicant a new production line would have to be opened and a new technology introduced.

The Confidential Annex to this AoA explains the challenges that the applicant would face in researching, trialling and starting the production of Akardite II at their plant. The conclusion is that the availability of the substance for the applicant is very unlikely to improve in the foreseeable future, without very significant investment, which in light of the size of the affected market, cannot be justified.

Additional confidential information is presented in: AoA Confidential Annex DBP Propellants DEZA.pdf, Section 4.1.4

Availability for the downstream users

Akardite II is already used in nitrocellulose-based propellant formulations and is generally available on the market for use by propellant manufacturers.

4.5.6 Conclusion on suitability and availability of Akardite II

4.5.6.1 Technical suitability

The substance is a phenyl urea the manufacture of which is based on precursors and technology completely unknown and wholly incompatible with the applicant's production plant. Akardite II cannot be considered technically feasible from the applicant's perspective.

From the perspective of the DUs, it could theoretically be used as a moderant but it is unusable as a plasticiser. Even as a moderant, Akardite II is a poorer moderant than DBP, as discussed in the Confidential Annex. Indeed, its current use in DBP-relevant propellant formulations is very limited. The issue of potentially carcinogenic N-nitroso decomposition products also casts doubts on the technical feasibility of the substance, although Akardites cause less concern compared to centralites.

4.5.6.2 Reduction in overall risk

As for Akardite I, the hazard profile of Akardite II is subject to a considerable measure of uncertainty, with significant knowledge gaps for the important endpoints of repeat dose toxicity and reproductive toxicity. Akardite II appears to have a more benign toxicological and ecotoxicological profile than DBP; however, it is classified as an eye irritant and raises concern with regard to its potential mammalian genotoxicity and acute aquatic toxicity. The potential carcinogenicity of the decomposition products formed in nitrocellulose-based plasticisers should be noted. As the risks from exposure to DBP from its use in the formulation and subsequent use of propellants are adequately controlled, the use of Akardite II would not result in discernible benefits to DUs' workers' health.

From the perspective of the applicant's workers, the precursors to Akardite II would appear to have unfavourable safety and human health hazard profiles and their handling and use would not confer any improvement to the working conditions for the applicant's staff.

4.5.6.3 Economic feasibility

The cost of establishing a production line for Akardite II would be extremely high and totally unjustified in light of the presence of established suppliers of the substance and the very modest sales that DEZA might potentially achieve. The lack of documented technical feasibility of the substance from the perspective of the DUs, cannot create any optimism that potential sales would allow DEZA to make a profit from a new production line.

4.5.6.4 Availability

From the perspective of the applicant, the substance is not available as its manufacture is based on technology and precursors not available to him. Availability is not expected to improve into the future; the quantity of Akardite II that would be sold by DEZA is too small to justify the expense of setting up and operating a new production line based on new technology.

From the perspective of the DUs, the substance appears to be generally available on the market.

Key point 13

Akardite II is not a realistic alternative for the applicant. Its technical feasibility for DUs is uncertain and its economic feasibility is poor. Its hazard profile shows significant information gaps

e) ALTERNATIVE SUBSTANCE: AKARDITE III (3-ETHYL-1,1,-DIPHENYL UREA)

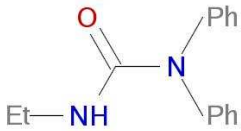
4.6 Akardite III

4.6.1 Substance ID and properties

4.6.1.1 Name and other identifiers for the substance

The following Table presents the identity of Akardite III.

Table 4.40: Identity of Akardite III

Parameter	Value	Source
EC number	242-052-9	1
EC name	3-ethyl-1,1-diphenylurea	1
CAS number	18168-01-9	1
IUPAC name	3-Ethyl-1,1-diphenylurea	2
Other names	Urea, N'-ethyl-N,N-diphenyl- N'-ethyl-N,N-diphenylurea	2
Molecular formula	$C_{15}H_{16}N_2O$	1
SMILES notation	O=C(N(c1ccccc1)c2ccccc2)NCC	2
Molecular weight	240.3	1
Molecular structure		1
Sources: *1: ESIS Internet site: http://esis.jrc.ec.europa.eu/* *2: Chemspider Internet site: http://www.chemspider.com/Chemical-Structure.26909.html*		

4.6.1.2 Composition of the substance

No information is available on constituents and impurities. The substance does not appear on ECHA's database of registered substances[26].

4.6.1.3 Physico-chemical properties

The following Table summarises the available information on the physicochemical properties of Akardite III. The information has been collected from a single literature source and consultation.

[26] Date of last search: 4 July 2013.

Table 4.41: Physicochemical properties of Akardite III

Property	Value	Remarks	Source
Physical state at 20°C and 101.3 kPa	Solid		
Melting/freezing point	149.16°C	MPBPWIN v1.42, Mean or Weighted MP (EPISuite)	1
	73.1°C or 89°C	Consultation response	
Boiling point	423.26°C at 101.3 kPa	ACD/Labs' ACD/PhysChem Suite	1
	400.62°C	MPBPWIN v1.42, Adapted Stein & Brown method (EPISuite)	1
Density	1.128 g/cm^3	ACD/Labs' ACD/PhysChem Suite	1
Vapour pressure	0 kPa at 25°C	ACD/Labs' ACD/PhysChem Suite	1
	5.85 x10^{-8}kPa	MPBPWIN v1.42, Modified Grain method (EPISuite)	1
Surface tension	46.58 dyne/cm	ACD/Labs' ACD/PhysChem Suite	1
Water solubility	221.4 mg/L at 25°C	WSKOW v1.41 (EPISuite)	1
	87.196 mg/L	Estimate from Fragments, Wat Sol (v1.01 est)	1
Partition coefficient n-octanol/water	2.44	KOWWIN v1.67 estimate (EPISuite)	1
Flash point	209.78 °C	ACD/Labs' ACD/PhysChem Suite	1
Flammability	No data		
Explosive properties	No data		
Self-ignition temperature	No data		
Oxidising properties	No data		
Granulometry	No data		
Source: *1: Chemspider Internet site: http://www.chemspider.com/Chemical-Structure.26909.html*			

4.6.1.4 Classification and labelling

An online search was performed using the CAS number in ECHA's C&L Inventory. No information has been retrieved[27].

4.6.1.5 REACH Registration details

The following Table summarises the available information on the status of REACH Registration of Akardite III.

Table 4.42: REACH Registration status of Akardite III

Registration	Result	Date of last search
Pre-registered	Yes – Envisaged Registration deadline: 30/11/2010	4 June 2012
Registered	No	20 June 2013
Source: *European Chemicals Agency: http://echa.europa.eu/*		

[27] Date of last search: 4 July 2013.

4.6.2 Technical feasibility

4.6.2.1 Technical feasibility from the perspective of the applicant

DEZA does not currently manufacture this substance and does not have any current plans to start production in the future without a clear indication from its DUs that Akardite III would be a technically feasible and acceptable alternative.

The Confidential Annex to this AoA explains that DEZA does not have access to the precursors to Akardite III and it is unclear whether these can be easily obtained and how they could be used within DEZA's plant.

Importantly, the manufacture of Akardite III is based on entirely different technology, which is not within DEZA's capabilities. DEZA's esterification plant can produce a range of phthalates (depending on the availability of precursor alcohols) and other esters, should the raw materials became available, but does not have the ability to manufacture phenyl ureas. Technically, this alternative cannot be considered feasible for the applicant.

Additional confidential information is presented in: AoA Confidential Annex DBP Propellants DEZA.pdf, Section 4.1.2

4.6.2.2 Technical feasibility from the perspective of downstream users

Relevance as substitute for DBP

According to consultation, the relevance of the substance as a substitute for DBP in propellant mixtures is as follows:

Substance family	Alkyl diphenyl ureas
Function	Moderant

Background to the use of the substance

Functions of Akardite III in propellants: literature suggests that Akardite III is a stabiliser for double-base propellants with a more pronounced plasticising effect than Akardite I (Meyer, Köhler, & Homburg, 2007).

Non-explosive uses of Akardite III: no information is available.

Comparison against key technical feasibility and selection criteria

Trials with the substance and perceived overall technical suitability: this information is presented in the Confidential Annex.

Comparison against the key technical feasibility and selection criteria: this information is presented in the Confidential Annex.

Other technical considerations: the issues associated with the generation of carcinogenic decomposition products when Akardites are used in nitrocellulose-based propellants would also apply here.

Additional confidential information is presented in: AoA Confidential Annex DBP Propellants DEZA.pdf, Section 4.6.2.2

4.6.3 Reduction of overall risk due to transition to the alternative

4.6.3.1 Hazard information

In the absence of any published information on the hazard profile of Akardite III, QSAR models (OECD QSAR toolbox and FDA EKDB models) were employed to derive additional insights into both the mammalian and ecotoxicological profile of this substance. The outputs of the modelling (and associated references) are presented in Table 4.43, overleaf. Based on all available information, the hazard profile of this substance may be summarised as follows.

Mammalian hazard profile

Acute toxicity: no information is available on the acute toxicity of Akardite III.

Repeat dose toxicity: no information is available on the repeat dose toxic potential of Akardite III.

Irritancy and sensitisation: two QSAR estimates of skin corrosivity/irritancy and one estimate for eye irritation were generated using the OECD toolbox. However, only one for the skin fell within its established domain. This indicated that it was not considered of concern with regard to severe irritancy. Overall, therefore, there appears to be no grounds for concern for these endpoints. No information is available on the sensitisation potential of Akardite III.

Genotoxicity and carcinogenicity: a series of QSAR predictions for in vitro prokaryotic mutagenic activity were consistently negative, as was a prediction based on a mammalian SHE assay. A prediction based on the mouse micronucleus assay was also negative. However, equivocal responses were predicted in QSAR models drawing on one mammalian cell line for mutagenicity and one based on a mouse bone marrow assay for chromosomal effects. Overall, however, there appears to be little concern with regard to the potential of Akardite III to cause genotoxicity. Similarly, a series of QSAR models for carcinogenicity indicated a low concern with regard to this endpoint.

Reproductive toxicity and developmental toxicity: no information is available on the reproductive or developmental toxicity of the substance.

Other toxicity: use of the FDA EKDB model to inform on the protein binding and oestrogenic and androgenic activity of Akardite III raised no alerts concerning the potential endocrine activity of the substance, although these predictions should not be considered robust and are therefore unsuited to drawing firm conclusions.

Environmental fate and behaviour and ecotoxicology

Available information from various QSAR models does not raise concerns as to the persistence or bioaccumulative potential of the substance in the environment.

No published experimental ecotoxicity data were identified, but QSAR predictions of its toxicity to aquatic organisms suggest that it is not acutely toxic to fish but could possible pose some measure of acute risk to invertebrate and bacterial species. The level of toxicity predicted for bacteria (EC_{50} = 0.0132 mg/L) would raise some concern with regard to the risk posed to micro-organisms.

Table 4.43: Human health and environmental hazard profile for Akardite III

Hazard endpoint		Finding	Data source	Study design	Assessed robustness/Comment
Toxicokinetics		Extent of absorption = 96.7%	OECD QSAR	QSAR prediction of human intestinal absorption by Multicase expert system	Result reported to be undefined with regard to domain applicability, hence considered of uncertain reliability
Irritation	Skin irritation/corrosion	Not corrosive to skin	OECD QSAR	QSAR prediction by Bundesinstitut für Risikobewertung (BfR) skin irritation/corrosion (for an undefined endpoint)	Result reported to be undefined with regard to domain applicability, hence considered of uncertain reliability
		Negative	OECD QSAR	QSAR prediction for severe skin irritation, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Not corrosive to skin	OECD QSAR	QSAR prediction by BfR skin irritation/corrosion model	Result reported to be undefined with regard to domain applicability, hence considered of uncertain reliability
	Eye irritation	Undefined	OECD QSAR	QSAR prediction by BfR eye irritation/corrosion	Result reported to be undefined with regard to domain applicability, hence considered of uncertain reliability
Genetic toxicity	In vitro - Mutagenicity	Negative	OECD QSAR	QSAR prediction based on Ames test (*S. typhimurium*), from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Negative	OECD QSAR	QSAR prediction based on Ames test (*S. typhimurium*), S9 activation status unspecified, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Negative	OECD QSAR	QSAR prediction by Ames test (*S. typhimurium*) with S9 metabolic activation, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Negative	OECD QSAR	QSAR prediction by Ames test (*S. typhimurium*) without S9 metabolic activation, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Negative	OECD QSAR	QSAR prediction by DNA reactivity (based on DNA reactivity assay using Ashby fragments, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable

Hazard endpoint		Finding	Data source	Study design	Assessed robustness/Comment
		Equivocal	OECD QSAR	QSAR prediction for Chinese Hamster Ovary (CHO) cell assay for chromosome aberration test, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
	In vitro – Chromosomal effect	Negative	OECD QSAR	QSAR prediction for sister chromatid exchange in Syrian Hamster Embryo (SHE) assay, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
	In vivo - Mutagenicity	No information			
	In vivo – Chromosomal effect	Equivocal	OECD QSAR	Prediction for mouse bone marrow sister chromatid exchange assay	Reported to be within QSAR domain, hence considered acceptable
		Negative	OECD QSAR	QSAR prediction by mouse micronucleus chromosome aberration assay, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
Carcinogenicity		Negative	OECD QSAR	QSAR prediction based on FDA Cancer Female Mouse, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Negative	OECD QSAR	QSAR prediction based on FDA Cancer Male Mouse, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Negative	OECD QSAR	QSAR prediction for Mouse Lymphoma, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Carcinogenic potency value (TD_{50}) = 1000 mg/kg	OECD QSAR	QSAR prediction for Mouse Carcinogenic Potency Database (CPDB), from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Negative	OECD QSAR	QSAR prediction based on FDA Cancer Female Rat, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Negative	OECD QSAR	QSAR prediction based on FDA Cancer Male Rat, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable

Hazard endpoint		Finding	Data source	Study design	Assessed robustness/Comment
		Carcinogenic potency value (TD_{50}) = 1000 mg/kg	OECD QSAR	QSAR prediction for Rat Carcinogenic Potency Database (CPDB), from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
Toxicity to reproduction		No information			
Developmental toxicity / teratogenicity		No information			
Other toxic endpoints	Protein binding potential	No alert found	OECD QSAR	QSAR prediction	No indication identified that model was operating outside of its operational limits
		No alert found	OASIS (in OECD QSAR)	QSAR prediction	No indication identified that model was operating outside of its operational limits
	Androgen receptor binding activity (RBA)	-2.25 to -1.73 log RBA	FDA EKDB model	Model drew comparison with linuron and hydroxylinuron	Model reports that on basis of only limited similarity with compounds in database (0.4-0.44), no conclusion should be drawn
	Oestrogen gene activation	-10000 TO -100 log RBA	FDA EKDB model	Model drew comparison with hydroxyflutamide, 4,4'-methylenebis(N,N-dimethylaniline) and M2	Model reports that on basis of only limited similarity with compounds in database (0.29-0.33), no conclusion should be drawn
	Oestrogen receptor binding activity (RBA)	10%	OECD QSAR	QSAR prediction by oestrogen receptor binding activity (Multicase)	Reported to be outside of QSAR domain, hence considered of doubtful reliability
		Negative	OECD QSAR	QSAR prediction by relative oestrogen receptor binding activity, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		-10000 TO -100 log RBA	FDA EKDB model	Model drew comparison with hydroxyflutamide, 4,4'-methylenebis (N,N-dimethylaniline) and M2	Model reports that on basis of only limited similarity with compounds in database (0.29-0.33), no conclusion should be drawn
Aquatic toxicity	Taxa not specified	0.0132 mg/L	OECD QSAR	QSAR estimation of behaviour endpoint by uTOX (Multicase)	Reported to be within QSAR domain, hence considered acceptable

Hazard endpoint		Finding	Data source	Study design	Assessed robustness/Comment
	Taxa not specified	Immobilisation EC_{50} = 0.0132 mg/L	OECD QSAR	QSAR estimation of immobilisation endpoint by uTOX (Multicase)	Reported to be within QSAR domain, hence considered acceptable
	Invertebrate	Immobilisation EC_{50} = 0.33 mg/L (48 hour)	OECD QSAR	QSAR estimation for *D. magna*, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
	Taxa not specified	EC_{50} = 0.0132 mg/L	OECD QSAR	QSAR estimation of mortality by uTOX (Multicase)	Reported to be within QSAR domain, hence considered acceptable
	Algae	EC_{50} = 0.764 mg/L (48 hour)	OECD QSAR	QSAR prediction for mortality in *P. subcapitata*, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
	Fish	LC_{50} = 44.5(4.21-469) mg/L (96 hour)	OECD QSAR	QSAR prediction for mortality in fathead minnow (*P. promelas)*, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
	Taxa not specified	0.0132 mg/L	OECD QSAR	QSAR estimation of undefined endpoint by uTOX (Multicase)	Reported to be within QSAR domain, hence considered acceptable
	Bacteria	EC_{50} = 0.0132 mg/L	OECD QSAR	QSAR estimation on *Vibrio fischeri* viability, by uTOX (Multicase)	Reported to be within QSAR domain, hence considered acceptable

Sources:
OECD QSAR Data obtained using OECD QSAR Toolbox at Internet site:
http://www.oecd.org/chemicalsafety/assessmentofchemicals/theoecdqsartoolbox.htm#Download_qsar_application_toolbox
FDA EKDB data obtained using FDA EKDB Database at Internet site:
http://www.fda.gov/ScienceResearch/BioinformaticsTools/EndocrineDisruptorKnowledgebase/default.htm

4.6.3.2 Comparison of hazards

The absence of any publicly available experimental data – particularly with regard to the acute and repeat dose toxicity and reproductive and developmental toxicity of Akardite III – together with the variable robustness of the QSAR predictions generated for some endpoints, significantly limits our ability to establish a hazard profile for this substance. However, tentatively it may be considered that, based on the available information, there appears to be little concern with regard to potential genotoxicity or carcinogenicity and it does not appear to pose a major concern with regard to either its environmental fate and behaviour, or ecotoxicity profile. As such, it might therefore be tentatively suggested that Akardite III may possess a more benign human and environmental hazard profile than DBP.

Table 4.44 below summarises our current limited understanding of the hazard profile of Akardite III, in comparison with that established for DBP. It should be stressed, however, that this assessment of Akardite III incorporates a considerable degree of uncertainty given the reliance on QSAR predictions and, importantly, the absence of any information on several critical human health endpoints.

Table 4.44: Hazard comparison of DBP and Akardite III

Hazard endpoint	Akardite III	DBP
Human health		
Acute toxicity		
Sensitisation		
Repeat dose		Toxic
STOT		Liver, kidney, testes
Reproductive toxicity		1B (male fertility)
Developmental toxicity		1B (males)
Carcinogenicity		Data are insufficient to determine the carcinogenic potential. No evidence of carcinogenicity is available. The CSR assumes that the substance is not a carcinogen
Environment		
Aquatic	Potentially toxic	Very toxic
Other		
Other issues	Potential for carcinogenic degradation products	
Note: grey cells indicate areas where no relevant information is available		

4.6.3.3 Safety issues with the manufacture of Akardite III

The Confidential Annex explains that the use of the precursors to Akardite III by the applicant would raise serious concerns. Based on hazard classifications and in comparison to the precursors to DBP:

- the carbonyl precursor is highly flammable, acutely toxic (by inhalation) and may cause skin and eye irritation; and
- the amine precursor is a skin and eye irritant.

The use of precursors to Akardite III would be unlikely to result in a lowering of existing hazards at the workplace for DEZA's workers.

Additional confidential information is presented in: AoA Confidential Annex DBP Propellants DEZA.pdf, Section 4.1.2

4.6.4 Economic feasibility

The discussion presented above for the other urea derivatives would similarly apply here.

DEZA does not and cannot manufacture Akardite III as it does not have the technology and expertise for doing so. The substance is foreign to DEZA's product portfolio and capabilities.

The Confidential Annex to this AoA explains that the manufacture of Akardite III could not make use of existing facilities at DEZA's DBP plant. An entire plant rebuild would be required with a cost that could amount to several millions of Euros and would require a timeline sufficiently long to make any thought of starting production completely unrealistic.

Importantly, due to the inherent technical infeasibility of the substance from the perspective of DUs, it is unclear whether any of them would actually use Akardite II as a substitute of DBP. Even if Akardite III would prove to be technically feasible for the applicant's customers, the volume of current sales of DBP to propellant manufacturers that could be substituted with Akardite III would only be very modest, due to the overall small tonnage of moderant that is required in the "Applied for" Use.

Overall, if Akardite III were to be chosen by DUs as a substitute for DBP in propellant formulations, DEZA would lose its entire sales of DBP in the field, as it would not be able to produce this substance. Information on DEZA's turnover that is associated with sales of DBP to propellant manufacturers is provided in the SEA (Section 2.2.2.1).

This alternative substance cannot be considered economically feasible for the applicant.

Additional confidential information is presented in: AoA Confidential Annex DBP Propellants DEZA.pdf, Section 4.1.3

4.6.5 Availability

4.6.5.1 Current and projected availability

Availability for the applicant

As discussed above, Akardite III is manufactured using technology that is alien to DEZA's current portfolio and capabilities. Phenyl ureas are not possible to manufacture at DEZA's DBP plant, as explained in the Confidential Annex to this AoA.

Availability for the downstream users

From the perspective of the DUs, the market availability of Akardite III is given in Table 4.45.

Table 4.45: Market availability of Akardite III

Alternative	Data availability	Market availability from the perspective of the downstream users
Akardite III	Very limited	Uncertain availability. Some consultees have experienced difficulty in sourcing the substance. Not REACH registered

4.6.5.2 Actions required for improving availability

Availability for the applicant

For Akardite III to become available to the applicant a new production line would have to be opened and a new technology introduced.

The Confidential Annex to this AoA explains the challenges that the applicant would face in researching, trialling and starting the production of Akardite III at their plant. The conclusion is that the availability of the substance for the applicant is very unlikely to improve in the foreseeable future, without very significant investment, which in light of the size of the affected market, cannot be justified.

Additional confidential information is presented in: AoA Confidential Annex DBP Propellants DEZA.pdf, Section 4.1.4

Availability for the downstream users

No specific information is available.

4.6.6 Conclusion on suitability and availability of Akardite III

4.6.6.1 Technical suitability

The substance is a phenyl urea the manufacture of which is based on precursors and technology completely unknown and wholly incompatible with the applicant's production plant. Akardite III cannot be considered technically feasible from the applicant's perspective.

From the perspective of the DUs, practical experience with the substance is extremely limited and suggestions of potential technical feasibility as a moderant are the result of informed assumptions and speculation rather than actual testing with the substance. The issue of potentially carcinogenic N-nitroso decomposition products also casts doubt on the technical feasibility of the substance, although Akardites cause less concern compared to centralites.

4.6.6.2 Reduction in overall risk

The absence of any publicly available experimental data – particularly with regard to the acute and repeat dose toxicity and reproductive and developmental toxicity of Akardite III, significantly limits our ability to establish a hazard profile for this substance. Based on the limited available information, it might therefore be tentatively suggested that Akardite III might possess a more benign human and environmental hazard profile than DBP. Concerns may arise in respect with the

generation of potentially carcinogenic N-nitroso decomposition products, although such issues may be less prominent in comparison to centralites. As the risks from exposure to DBP from its use in the formulation and subsequent use of propellants are adequately controlled, the use of Akardite III would not result in discernible benefits to DUs' workers' health.

From the perspective of the applicant's workers, the precursors to Akardite III would appear to have unfavourable safety and human health hazard profiles and their handling and use would not confer any improvement to the working conditions for the applicant's staff.

4.6.6.3 Economic feasibility

The cost of establishing a production line for Akardite III would be extremely high and totally unjustified in light of the very modest sales that DEZA might potentially achieve. The lack of documented technical feasibility of the substance from the perspective of the DUs, cannot create any optimism that potential sales would allow DEZA to make a profit from a new production line.

4.6.6.4 Availability

From the perspective of the applicant, the substance is not available as its manufacture is based on technology and precursors not available to him. Availability is not expected to improve into the future; the quantity of Akardite III that would be sold by DEZA is too small to justify the expense of setting up and operating a new production line based on new technology.

From the perspective of the DUs, some concerns have been expressed as to whether obtaining the substance on the market is easy.

Key point 14

Akardite III is not a realistic alternative for the applicant. Its technical feasibility for DUs is uncertain and its economic feasibility is poor. Its hazard profile is largely unknown

f) ALTERNATIVE SUBSTANCE: BIS(2-ETHYLHEXYL) ADIPATE

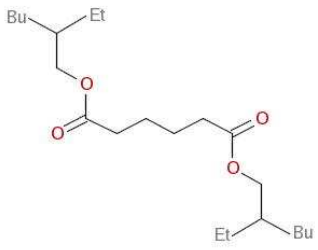
4.7 Bis(2-ethylhexyl) adipate

4.7.1 Substance ID and properties

4.7.1.1 Name and other identifiers for the substance

The following Table presents the identity of DEHA.

Table 4.46: Identity of DEHA

Parameter	Value	Source
EC number	203-090-1	1
EC name	Bis(2-ethylhexyl) adipate	1
CAS number	103-23-1	1
IUPAC name	Bis(2-ethylhexyl) adipate	1
Other names	Di-octyl-adipate (DOA) Hexanedioic acid, bis (2-ethylhexyl) ester Adipic acid, bis (2-ethylhexyl) ester Di-2-ethylhexyl hexane-1,6-dioate	1,2
Molecular formula	$C_{22}H_{42}O_4$	1
SMILES notation	O=C(OCC(CC)CCCC)CCCCC(=O)OCC(CCCC)CC	2
Molecular weight	370.5665	2
Molecular structure		3

Sources:
1: European Chemicals Agency: http://echa.europa.eu/
2: ChemSpider Internet site: http://www.chemspider.com/Chemical-Structure.7358.html
3: ESIS Internet site: http://esis.jrc.ec.europa.eu/

4.7.1.2 Composition of the substance

No information is available on constituents or impurities of the commercially available substance, including in the ECHA Dissemination Portal[28]. However, a search of the Internet reveals several commercially available DEHA products with purity of >98%[29].

[28] Date of last search: 5 July 2013.

[29] See for example: http://www.chemexper.com/chemicals/supplier/cas/103-23-1.html (accessed on 15 February 2013).

4.7.1.3 Physico-chemical properties

The following Table summarises the available information on the physico-chemical properties of DEHA. The information has been collected from a single literature source and consultation.

Table 4.47: Physico-chemical properties of DEHA

Property	Value	Remarks	Source
Physical state at 20°C and 101.3 kPa	Liquid		1
Melting/freezing point	-67.8°C	Measured; Lide DR (1998): CRC Handbook of Chemistry and Physics, 79th ed. Boca Raton, FL: CRC Press Inc. (cited in HSDB)	1
Boiling point	417°C at 1013.25 hPa	Measured; SRC PhysProp (2008), Syracuse Research Corporation Database	1
Density	0.92 g/cm³ at 20°C	DIN 51757, pycnometer method	1
Vapour pressure	3 x10^{-8} kPa at 20°C	Estimated value through graphic extrapolation analogous to the vapour pressure of tetracosane	1
	1.13 x10^{-7} kPa at 20°	Felder J.D. et al. (1986): Environmental Toxicology and Chemistry, Vol. 5, pp. 777-784	1
Surface tension	32.23 dyne/cm	Predicted data is generated using the ACD/Labs' ACD/PhysChem Suite	2
Water solubility	0.0032 mg/L at 22°C	Felder, JD, Adams, WJ & Saeger, VW (1986): Assessment of the Safety of Dioctyl Adipate in Freshwater Environments, Environ. Toxicol. Chem. Vol 5, pp. 777-784	1
	0.78 mg/L at 22°C		1
Partition coefficient n-octanol/water	8.94 at 25 °C	OECD Guideline 117 (Partition Coefficient (n-octanol / water), HPLC Method)	1
Flash point	196°C at 1013.25 hPa	Closed cup Database from Berufsgenossenschaftliches Institut für Arbeitsschutz, dated 2007	1
	196°C at 1013.25 hPa	Lewis, R.J. Sr. (1993): Hawley's Condensed Chemical Dictionary, Twelfth Edition, p. 394, Van Nostrand Reinhold	1
	206°C	Cleveland closed cup	3
Flammability	Not relevant		1
Explosive properties	Not relevant		1
Self-ignition temperature	377°C at 1013.25 hPa	Measured National Fire Protection Association (1997): Fire Protection Guide to Hazardous Materials 12ed., Quincy, MA: National Fire Protection Association, p. 325-44 (cited in HSDB)	1
	340°C at 1013.25 hPa	Measured GESTIS Database, Berufsgenossenschaftliches Institut für Arbeitsschutz	1
Oxidising properties	No oxidising properties		1
Granulometry	Not relevant		1

Sources:
1: European Chemicals Agency: http://echa.europa.eu/
2: ChemSpider Internet site: http://www.chemspider.com/Chemical-Structure.7358.html
3: (Unitex, 2004)

4.7.1.4 Classification and labelling

An online search using the substance's CAS number was undertaken on ECHA's C&L Inventory[30]. No information on harmonised classification and labelling for DEHA is available; 796 notifiers did not submit a classification. The ECHA Dissemination Portal similarly does not indicate any classification was required. However, according to the Inventory, nine aggregated notifications have been made. These are presented in Table 4.48.

Table 4.48: Notified classification and labelling of DEHA according to CLP criteria

Classification		**Labelling**		**Number of Notifiers**
Hazard Class and Category Code(s)	**Hazard Statement Code(s)**	**Hazard Statement Code(s)**	**Pictograms Signal Word Code(s)**	
Skin Irrit. 2	H315	H315 (Causes skin irritation)	GHS07 GHS09 Wng	23
Eye Irrit. 2	H319	H319 (Causes serious eye irritation)		
Aquatic Acute 1	H400	H400 (Very toxic to aquatic life)		
Aquatic Acute 1	H400	H400 (Very toxic to aquatic life)	GHS09 Wng	11
Aquatic Chronic 1	H410	H410 (Very toxic to aquatic life with long lasting effects)		
Aquatic Acute 1	H400	H400 (Very toxic to aquatic life)	GHS09 Wng	6
Skin Irrit. 2	H315	H315 (Causes skin irritation)	GHS07 GHS09 Wng	4
Eye Irrit. 2	H319	H319 (Causes serious eye irritation)		
Aquatic Acute 1	H400	H400 (Very toxic to aquatic life)		
		H312 (Harmful in contact with skin)	GHS06 GHS09 Dgr	1
Acute Tox. 4	H302	H302 (Harmful if swallowed)		
Skin Irrit. 2	H315	H315 (Causes skin irritation)		
Eye Irrit. 2	H319	H319 (Causes serious eye irritation)		
Acute Tox. 2	H332	H332 (Harmful if inhaled)		
Aquatic Acute 1	H400	H400 (Very toxic to aquatic life)		
Carc. 2	H351	H351 (Suspected of causing cancer)	GHS08 Wng	1
Repr. 2	H361	H361 (Suspected of damaging fertility or the unborn child)	GHS08 Wng	1
Aquatic Acute 1	H400	H400 (Very toxic to aquatic life)	GHS09 Wng	1
Aquatic Chronic 2	H411	Toxic to aquatic life with long lasting effects		
Blank entry				1

4.7.1.5 REACH Registration details

The following Table summarises the available information on the status of REACH Registration for DEHA.

[30] Date of last search: 5 July 2013.

Table 4.49: REACH Registration status of DEHA

Registration	Result	Date of last search
Pre-registered	Yes	2 November 2012
Registered	Yes –10,000–100,000 t/y	20 June 2013
Source: *European Chemicals Agency: http://echa.europa.eu/*		

4.7.2 Technical feasibility

4.7.2.1 Technical feasibility from the perspective of the applicant

The applicant currently manufactures this substance in quantities sufficient for supplying their existing customers in the field of propellants. Technically, this alternative is feasible for the applicant.

4.7.2.2 Technical feasibility from the perspective of downstream users

Relevance as substitute for DBP

According to consultation, the relevance of the substance as a substitute for DBP in propellant mixtures is as follows:

Substance family	Adipate esters
Function	Plasticiser

Background to the use of the substance

Functions of DEHA in propellants: the use of DEHA as a plasticiser in gun propellants has been confirmed in literature (Damse & Singh, 2008). Other adipates have also been identified as relevant to propellants such as di-n-propyl adipates and polyglycol adipates.

DEHA may also be used in rocket propellants as a plasticiser (Ledgard, 2006) (Ledgard J. , 2007) and as a binder in plastic bonded explosives (IPI, 2011b) (BlastGard, 2008).

Non-explosive uses of DEHA: information is available from the registration dossier for DEHA, which is available from the ECHA Dissemination Portal[31]. The substance is commonly used as a plasticiser for PVC, for the manufacture of PVC articles by calendering, spread coating, etc. (including for food contact and medical applications) but also through the manufacture of plastisols. DEHA has numerous PVC applications in toys, vinyl flooring, wire and cable, stationery, wood veneer, coated fabrics, gloves, tubing, artificial leather, shoes, sealants, and carpet backing. It is also used in films employed in food packaging materials, fillers, paint and lacquers, adhesives, plastic in concrete, and rubber products. Future applications are expected to include products for the hospital sector and printing inks, essentially as substitutes for phthalate esters (Lowell Center for Sustainable Production, 2011).

[31] Information available from: http://apps.echa.europa.eu/registered/data/dossiers/DISS-a134506c-6383-58e2-e044-00144f67d031/AGGR-f8bd7790-6b58-472f-8df1-fef99bc4cd5d_DISS-a134506c-6383-58e2-e044-00144f67d031.html#section_3_5 (accessed on 5 July 2013).

Other materials commonly plasticised with DEHA include rubber, acrylates and nitrocellulose, cellulose butyrate, polyvinyl pyrrolidone, nitrile rubber, polyurethanes, and cosmetics (curable nail coating) (Wypych, 2004).

DEHA is also used in the formulation of lubricants and adhesives and as a viscosity modifier in fragrances.

Comparison against key technical feasibility and selection criteria

Trials with the substance and perceived overall technical suitability: this information is presented in the Confidential Annex.

Comparison against the key technical feasibility and selection criteria: this information is presented in the Confidential Annex.

Additional confidential information is presented in: AoA Confidential Annex DBP Propellants DEZA.pdf, Section 4.7.2.2

4.7.3 Reduction of overall risk due to transition to the alternative

4.7.3.1 Hazard information

The ECHA Dissemination Portal, together with other publicly available sources, provides a good insight into most aspects of the mammalian and ecological hazards posed by DEHA. As a result, only limited recourse to QSAR modelling (OECD QSAR toolbox and FDA EKDB models) was undertaken to inform on the substances potential for interacting with the endocrine system (the outputs of the modelling are presented in Table 4.50).

Table 4.50: QSAR output for potential endocrine related effects for DEHA

Hazard endpoint	Finding	Data source	Study design	Assessed robustness/Comment
Protein binding potential	No alert found	OECD QSAR	QSAR predictions based on OASIS and OECD models	Not possible to classify based on model's rules, hence not considered reliable
Androgen receptor binding activity	-10000 log RBA	FDA EKDB model	Information based on di(2-ethylhexyl) adipate (not read across)	Model considered to be operating within domain, hence considered reliable
Estrogen gene activation	-10000 log RP	FDA EKDB model	Information based on di(2-ethylhexyl) adipate (not read across)	Model considered to be operating within domain, hence considered reliable
Estrogen receptor binding activity	0	OECD QSAR	QSAR prediction for rat estrogen receptor binding affinity from Fang et al. Chem. Res. Tox., 14,280-294 (year not reported), from OASIS database	No information on conformity with QSAR model's domain characteristics reported, hence of uncertain reliability
	10%	OECD QSAR	QSAR prediction by estrogen receptor binding activity (Multicase)	Reported to be outside of QSAR domain, hence considered of doubtful reliability
	-10000 log RBA	FDA EKDB model		Model reports that DEHA is not active
Sources: *OECD QSAR Data obtained using OECD QSAR Toolbox at Internet site:* *http://www.oecd.org/chemicalsafety/assessmentofchemicals/theoecdqsartoolbox.htm#Download_qsar_application_toolbox* *FDA EKDB data obtained using FDA EKDB Database at Internet site:* *http://www.fda.gov/ScienceResearch/BioinformaticsTools/EndocrineDisruptorKnowledgebase/default.htm*				

Based on all available information, the hazard profile of this substance may be summarised as follows.

Mammalian hazard profile

Toxicokinetics: based upon experimental data, it appears that DEHA is rapidly and completely absorbed from the gastrointestinal tract, undergoing extensive GI tract hydrolysis (SCENIHR, 2008), a conclusion supported by the three key unpublished oral gavage studies (all Klimisch Score 1) cited in the ECHA Dissemination Portal. Each of these studies involved use of radiolabelled material (^{14}C-DEHA) at a dosage of 500 mg/kg bw in F344 rats and Cynomolgus monkeys, and 50, 500 and 5,000 mg/kg in B6C3F1 mice. The studies were conducted using protocols similar to OECD Guideline 417 and were conducted to GLP. The study in mice showed ^{14}C-DEHA and/or its metabolites were rapidly absorbed with the highest ^{14}C levels occurring in blood and liver after 1 or 3 hours. In the GI tract, large amounts of diester (DEHA), monoester (MEHA) and alcohol (EH) were present, while hepatic metabolites were more polar; furthermore, the metabolite profiles showed clear sex differences. Overall, about 91% urinary elimination was achieved at 50 or 500 mg/kg but only 75% at 5,000 mg/kg by 24 hours. Faecal elimination accounted for 7-8% at the low or intermediate dosage and 4% at the high dosage. A small amount was eliminated by expiration. In rats, male metabolite levels were higher than in females, with the highest concentration of radioactivity occurring in the GI tract 24 hours after dosing (comprising mainly the diester, monoester, alcohol and a trace of polar material), followed by liver (oxidation products), adrenals, kidneys, fat, and skin. Most of the blood radioactivity was recovered in plasma. Urine contained 2-ethylhexanoic acid (EHA), the glucuronic acid conjugate, a hydroxy acid (5-hydroxy-2-ethylhexanoic acid, 5-OH EHA), and a diacid (2-ethyl-1,6-hexanedioic acid, DiEHA). Overall, 95% of the administered dose was excreted by 24 hours. In the monkey, radioactivity quickly reached the blood stream, peaking 2 hours after dosing (the earliest sampling time investigated) followed by evidence of rapid systemic distribution, including particularly to the skin, fat and liver. Males showed a more rapid excretion, particularly during the first 6 hours, than females, though in each sex urinary elimination predominated accounting for 89-90% of the total.

A 1993 publication of a study in which six male volunteers were given 46 mg of DEHA dosed in corn oil via a gelatine capsule (Klimisch Score 2), is also available. This, while identifying no adverse responses, showed unconjugated [2H10]EHA was the only compound present at measurable quantities in plasma though [2H10] EH was detectable at below the limit of quantification. [2H10] EHA was found to be the principal metabolite in the urine, although [2H5]5-OH-EHA, [2H5] DiEHA, [2H5]EH and [2H5]keto-EHA were also present. The rate of elimination was similar for all metabolites, giving an overall elimination half-life (t½) of 1.5 hours.

Acute toxicity: the key acute oral toxicity study followed a design similar to OECD TG 401, but not to GLP, in Fischer 344 rats. In this, animals were given doses at up to 20 g/kg bw. Oral LD_{50} values of ca. 45,000 mg/kg bw (males) and ca. 24,600 mg/kg bw (females) were reported. Other supporting studies considered of relevance here indicated the LD_{50} value to be ca. 22,500 mg/kg bw in both sexes of rat, and 15,000 mg/kg bw (males) and ca. 24,600 mg/kg bw (females) in mice. Further studies in rabbits and cats of limited designs – such that they are difficult to interpret – also indicated limited acute toxicity. An acute inhalation study to OECD TG 403 and EU Method B.2 (Klimisch Score 1) in Wistar rats suggested a 4 hour inhalation LC_{50} of > 5.7 mg/L air. These results are supported by the conclusions of SCENIHR (2008) that considered DEHA to show very

low acute toxicity (LD_{50} = 7.4-45.0 g/kg bw) while the OECD SIDS for this substance[32] suggests that dermal exposure has no effects at dosages in excess of 2,000 mg/kg.

Irritancy and sensitisation: the ECHA Dissemination Portal presents arguments based on read across from a BUA 1996 study (Klimisch Score 2) which reports an in vivo test on the white rabbit for 'Plastomoll DNA' as the basis for considering DEHA to be not irritating. Similarly, read across for eye irritation is made from an OECD Guideline 405 study (Klimisch Score 1) for Plastomoll DNA in the white rabbit, which gave a primary irritation index of 1. These conclusions are, in general, in line with other assessments. For example, the OECD SIDS concludes that there is evidence that dermal irritation following prolonged exposure (24 hours) is slight and that shorter periods do not result in irritation and should not be considered to demonstrate eye irritation, while SCENIHR (2008) note that DEHA has been reported to be non-irritating or slightly irritating to the skin of rabbits.

With regard to sensitisation, two reports (again drawing on the 1996 BUA report) and a QSAR model (all judged Klimisch Score 2) are used to support weight of evidence arguments that DEHA is not a sensitiser, a conclusion further supported by SCENIHR (2008), OECD SIDS and Environment Canada (2011).

Repeat dose toxicity: two key studies are presented within the ECHA Dissemination Portal. In the first study, published in 2006, conducted using a design similar to a draft of the enhanced OECD TG407 and to GLP (Klimisch Score 2), Sprague-Dawley rats were orally gavaged with DEHA at 0, 40, 200 or 1,000 mg/kg/day for at least 28 days. In-life examinations identified no responses to treatment but post mortem examination showed, in males, increased body weight-relative kidney weight without associated histopathological change at 200 mg/kg/day, while at 1000 mg/kg/day, increased body weight-relative kidney weight and increased renal eosinophilic and hyaline droplets were noted for both sexes. Increased liver weight was also noted at the high dosage in males and females though no associated pathology is reported. However, another study (Klimisch Score 2) reported under 'Special investigations' in the Dissemination Portal compared the activity of several peroxisome proliferators and found that, in rats and mice given up to 2% DEHA in the diet for 30 days, peroxisome proliferation was apparent.

Another study into the hepatic toxicity of DEHA in the mouse and rat (Klimisch Score 1) in which animals were fed diets containing 0, 0.012, 0.12, 1.2 or 2.5% DEHA for up to 21 days (giving average intakes in mice of 32, 325, 3322 or 6370 mg/kg/day respectively and, in rats, 11, 122, 1177 or 2275 mg/kg/day) also found a significant increase in liver-weights of animals given 1, 2 or 2.5% DEHA. Histochemical examination of rat livers showed a dose-related reduction in periportal fat deposition in all treated groups and reduced cytoplasmic basophilia at 2.5% DEHA, a change associated with a moderate increase in peroxisome numbers. A slight rise in peroxisome numbers was also detectable in the 1.2% group with marginal increases apparent at 0.12%. In the mice, there was essentially little difference in neutral fat deposition in the controls and those given 0.012 or 0.12% DEHA, although fat deposition was largely centrilobular. Feeding 1.2 or 2.5% DEHA resulted in reduced centrilobular fat accompanied by the presence of fat deposits in the periportal region (considered likely to be artifactual in nature and, hence, probably should be discounted). There was a moderate increase of hepatic peroxisome numbers in hepatocytes from the 1.2 or 2.5% mouse groups but no changes at the 0.12% level (average intake 325 mg/kg/day), though an intake of 122 mg/kg/day resulted in a slight increase in peroxisome numbers. Generally, the effects of DEHA were found to be reversible following 14 days of withdrawal of treatment, though, for mice,

[32] Available at: http://www.inchem.org/documents/sids/sids/103231.pdf (accessed on 27 February 2013).

some hepatocytes adjacent to the centrilobular vein still contained increased peroxisomes. Further examination of the animals suggested the peroxisome response to be potentially mediated via a DNA-linked mechanism. A series of other studies (not discussed here in detail) also reported under 'Special investigations' provide additional support that DEHA is a peroxisome proliferator in rodent species. Although not discussed in the entry on the ECHA Dissemination Portal in respect of repeat dose toxicity, an increase in ovarian follicular atresia was also reported at the high dosage of the first key study. Based on the lack of associated renal pathology at 200 mg/kg bw/day, the kidney organ weight change was discounted at this dosage, which was suggested to constitute the NOAEL for this study.

The other key study presented relates to the non-neoplastic effects seen in response to dietary administration at 0, 12,000 or 25,000 ppm (equivalent to 0, 600 or 1250 mg/kg bw/day) to Fischer 344 rats over 103 weeks using a design similar to OECD TG 451; the neoplastic findings for this study are discussed below in relation to the carcinogenicity of DEHA. The only evidence of non-neoplastic response was a reduction in body weight gain in rats given the high dosage. Thus, the NOAEL was established at 12,000 ppm, equivalent to 600 mg/kg bw/day.

Other supporting studies are also presented which appear to be derived from the same paper and to be dose-range finding investigations to determine exposure levels for a carcinogenicity study using various species that were given DEHA at various dietary levels. As they add little to the understanding of the repeat dose toxicity profile of DEHA beyond that provided by the above discussed robust repeat dose investigations, they will not be considered further here.

The SIDS Initial Assessment Report (from OECD) for this substance notes that repeated-dose dietary toxicity studies of up to 90-days exposure in rats and mice identified reduced body weight gain at approximately 400 mg/kg bw/day or above in rats, and at approximately 600 mg/kg bw/day or above in mice, leading to suggested sub-chronic NOAELs of 189 mg/kg/day in rats and 451 mg/kg/day in mice when given via the oral route.

One unreliable repeat dose study in which the effects of dermal application were investigated by Hodge *et al*. (1966) is also mentioned on the ECHA Dissemination Portal (Klimisch Score 3) but no findings are discussed.

Genotoxicity and carcinogenicity: the ECHA Dissemination Portal identifies three key (Klimisch Score 2) and three supporting studies on the in vitro genotoxicity of DEHA. These include: a bacterial reverse mutation assay at up to 10,000 µg/plate in *S. typhimurium* strains TA 1535, TA 1537, TA 98 and TA 100, in the presence or absence of metabolic activation (S9 mix) and using a positive control, in a design similar to OECD TG 47; a mouse lymphoma L5178Y cells mutation assay similar to OECD TG 476 at up to a nominal level of 5,000 µg/ml (precipitation was observed at 1,000 µg/ml but the test was also conducted at 5,000 µg/m) by McGregor (1988); and a Chinese Hamster ovary (CHO) cell assay at 40-400 µg/mL for chromosomal effects reported by Galloway et al. (1987). The bacterial mutagenesis study was negative while a significant increase in mutant was noted in one replicate but not in another, though clear cytoxicity was noted. The CHO assay gave ambiguous results when no metabolic activation was used. Conclusions from a supporting study (a L5178Y mouse lymphoma assay) showed no significant adverse response and sister chromatid exchange (SCE) results for another CHO assay, identified as a supporting study, were negative without metabolic activation but equivocal in the presence of metabolic activation for CHO cells. A further negative *S. typhimurium* assay was also presented. In the key in vivo bone marrow micronucleus study in B6C3F1 mice (Shelby *et al*., 1993; Klimisch Score 2) using daily dosages of

375, 750, 1,500 and 2,000 mg/kg ip[33] for 3 days, the response was negative. A B6C3F1 mouse study at a dose up to 5 g/kg, that complied with OECD Guideline 474 and CLP, reported no significant differences in percent micronucleated PCEs[34] between treated and negative control animals; the study was judged to warrant Klimisch Score 1, though for some reason is reported as a supplementary rather than a key study. Overall, it appears that DEHA should be regarded as negative for mutagenic and for clastogenic potential, reflecting the opinion of the CSTEE noted by SCENIHR (2008) and the opinion of Environment Canada (2011).

With regard to carcinogenicity, two key studies are presented in the ECHA Dissemination Portal. In one, a 103 week dietary study in which animals were fed a diet at concentrations designed to achieve dosages of 600 or 1,250 mg/kg bw/day in the Fischer 344 rat and which was of a design similar to OECD Guideline 451, there were no significant increases relative to the tumour incidence found in the negative controls (Klimisch Score 2). It is also noted that the mean body weight of high-dose animals was lower than controls though no comment is made of intergroup survival or why the study was apparently of 103 weeks, as opposed to the guideline requirement of 104 weeks duration. In contrast, a key OECD TG 451 study (supplemented by inclusion of urinalysis, haematological and clinical biochemistry investigations) but again with treatment via the diet for 103 weeks (not 104 weeks and followed by a 4 week period of withdrawal from treatment) at concentrations resulting in dosages of 1,715 and 3,570 mg/kg bw in B6C3F1 mice (Klimisch Score 2), found increased incidences of hepatocellular carcinoma and hepatocellular adenoma in high dose treated animals (hepatocellular adenoma incidence of 5/50 in females but no significant effect reported in males, and, for hepatocellular carcinoma, incidence of 14/50 in females and 20/49 in males). These studies appear to originate from the same 1982 reporting source though no reference citation is provided by the registrant in their Portal entries.

There is thus clear evidence of hepatic carcinogenic effects in mice but not in rats. Given the absence of any significant genotoxic potential and in the light of the evidence on its repeat dose toxicity and the evidence in both rat and mouse species to suggest DEHA may be a peroxisome proliferator, however, it is likely that the carcinogenic effect may operate via a non-genotoxic mechanism and not of direct relevance to humans. In this respect, the basis on which the entry on the C&L Inventory by a single notifier that DEHA may warrant classification as Carcinogenic Category 2 H351 is unclear..

Reproductive and developmental toxicity: the reproductive toxicity of DEHA is informed on the ECHA Dissemination Portal by one key experiment, though a number of supporting studies are also mentioned. In the key study – which was conducted using a design similar to OECD TG 415 and to GLP (Klimisch Score 1) – diets containing DEHA at concentrations of 0 (untreated control), 300, 1,800 or 12,000 ppm were fed to male and female Wistar rats for up to 10 weeks, resulting in animals receiving nominal dosages of 0, 28, 170 or 1,080 mg/kg bw/day. In addition to recording clinical signs and body weight performance, a number of reproductive endpoints (length of gestation and of pre-coital interval) and offspring viability performance (live born index, survival index, litter size, total litter weight and whole litter loss) were recorded. In the F0 (parental) generation, the NOAEL based on absolute liver weight change in both sexes and body weight gain impairment in females) was established at 170 mg/kg bw/day (nominal) though no impact on reproductive parameters was indicated. Of the three supporting studies identified, in one published study (Mityata et al., 2006, conducted to OECD TG 422 and GLP) in Sprague-Dawley rats orally

[33] ip – Intra-peritoneal injection administration.

[34] PCE - Polychromatic erythrocyte.

gavaged at 40, 200 or 1,000 mg/kg/day for at least 28 days (Klimisch Score 2), a NOAEL for the F0 generation of 200 mg/kg bw/day was established in females. Some evidence of reproductive toxicity, namely increased ovarian follicle atresia and abnormal oestrous cycling, were noted in some rats at 1,000 mg/kg. For males, only non-reproductive effects (increased eosinophilic bodies and hyaline droplets in the kidneys) were noted for the 1,000 mg/kg group. As the other supporting studies were considered to warrant Klimisch Score 3, they have not been considered further here.

Although the key study above reports there to be no evidence of reproductive effects on parental animals even at a dose that elicits mild systemic toxicity, the supplementary study – which appears reasonably robust – provides some suggestion of reproductive toxic changes in females at 1,000 mg/kg bw/day, although 200 mg/kg/day appears to constitute the NOAEL. The OECD SIDS Initial Assessment Report reports there to be no evidence of reproductive toxicity associated with DEHA but SCENIHR (2008) noted the findings of the study by Mityata *et al*. (2006).

Developmental effects are considered in one key study on the ECHA Dissemination Portal conducted to GLP and of a design similar to OECD TG 414 (Klimisch Score 1). This showed several similarities to the OECD TG 415 study reported above, including use of the same rat strain and treatment levels. Against a reported NOAEL for maternal toxicity of 170 mg/kg bw/day (nominal), developmental toxicity findings comprised minimal foetotoxicity (reduced ossification and increase in incidence of visceral variants) giving a nominal NOAEL of 28 mg/kg bw/day; the authors interpretation was that these changes did not represent a significant adverse outcome.

The above referenced study judged 'key' for reproduction also provides further insight into possible developmental concerns though this is not specifically referred to in the Dissemination Portal. In this, the NOAEL for developmental effects in the F1 generation was reported as 170 mg/kg bw/day (nominal) based on effects on pup and litter weights which were noted to be present throughout the postnatal period at 12,000 ppm (1,080 mg/kg/d) and a slightly reduced mean litter size at this dosage. A further 1973 study is mentioned in the Dissemination Portal (Klimisch Score 2) but relates to a non-relevant route of administration and, hence, may be considered of little relevance here though it did report a NOAEL of only 9.2 mg/kg bw/day based on findings of gross, skeletal and visceral abnormalities and foetal size impairment. Mean foetal weights in the mid- and high-dose groups were significantly lower than controls though there were no skeletal effects identified.

In their review, SCENIHR (2008) note that CSTEE (1999) had identified several studies demonstrating a foetotoxic potential of DEHA, with one establishing a maternal NOAEL of 800 mg/kg bw/day and a developmental NOAEL of 200 mg/kg of DEHA, with prolonged gestation occurring at 800 mg/kg. Furthermore, the OECD SIDS Initial Assessment Report also reports a 1988 study (citing CEFIC as the source) that found pre-implantation foetal losses occurred at 1,080 mg/kg/day in the absence of gross, skeletal or visceral abnormalities. Slight foetotoxicity was, however, reported at 170 mg/kg/day in the form of reduced ossification but 28 mg/kg/day was again determined to be the NOAEL. The US EPA also suggested a NOAEL of 170 mg/kg/day.

The OECD SIDS Initial Assessment Report notes that during metabolism DEHA may be hydrolysed to adipic acid and 2-ethylhexanol, the latter is then oxidised to the established developmental toxin ethylhexanoic acid (EHA).

Overall, therefore, the reproductive and developmental hazard posed by DEHA is an area of uncertainty though it is important to note that reproductive changes have only been seen at relatively high exposures though there is some indications that it may cause developmental changes at somewhat lower dosages, with this being mediated potentially via a toxic metabolite. In this respect, the substance was listed in March 2013 for Substance Evaluation with respect to its potential CMR status, in part because of concerns regarding its reprotoxic potential.

Other toxicities: use of OECD QSAR toolbox and FDA QSAR models for the ability of DEHA to interact with proteins, the oestrogen or androgen receptors or the oestrogen gene, raised no concern with regard to the activity of DEHA in respect of these parameters. It should, however, be noted that in the case of the protein binding and oestrogen receptor binding activity models, there is some doubt as regards the robustness of the predictions generated by the available models.

Ecotoxicological Hazard Profile

Aquatic Toxicity

The aquatic toxic potential of DEHA is informed by a key acute study in fish (*O. mykiss*) undertaken according to test guideline EPA-66013-75-009 (Klimisch Score 2), which suggests a 96 h LC_0 of >0.78 mg/L. This study included test concentrations in excess of 100 times DEHA's water solubility (0.78 +/- 0.16 mg/L) without causing deaths. A supporting screening study in fish (*Leuciscus idus*) (Klimisch Score 2) also found a lack of toxicity in excess of DEHA's water solubility, reporting LC_{50} (4, 24 and 48h) values of >10,000 mg/L. No long-term studies of aqueous fish toxicity are, however, available.

A key study on invertebrates is presented in the ECHA Dissemination Portal (Klimisch Score of 2) undertaken to European test guideline (Directive 79/831/EWG, appendix V, part C2) and similar to OECD TG 202 in Daphniad. This reports an immobilisation EC_{50} (3, 6, 24 and 48 hour) of >500 mg/L, the highest nominal test concentration. Further invertebrate studies on the Portal inform on chronic toxicity in aqueous species. The key study (Klimisch Score 2) is undertaken to OECD TG 211 in *D. magna*, cited as OECD Guideline 202, part 2 (Daphnia sp., Reproduction Test). This gave 21 day NOEC and LOEC values of ≥0.77 mg/ and > 0.77 mg/L respectively indicating that the chronic and reproductive toxicity in daphnids are above the aqueous solubility. The supporting study (Klimisch Score 2) undertaken according to Draft No.3, of ASTM[35] E-47.01 relates to a flow-through test again in *D. magna* which found reduced yields of young per adult at mean measured concentrations of 0.087 or 0.18 mg/L. A maximum acceptable toxicant concentration (MATC) for chronic toxicity in *D.magna* was derived at 0.024 - 0.052 mg/L, based on adult mean length, survival and young per adult per reproductive day. It was concluded that the geometric mean of the LOEC and NOEC was 0.035 mg/L, approximately ten-fold above DEHA's solubility limit.

Information is also available on the toxicity to aquatic algae and cyanobacteria in the form of one key study in the dissemination portal undertaken according to Guideline DIN 38412, part 9 (Klimisch Score 2), in *Desmodesmus subspicatus*. A 72 hour EC_{50} for biomass of >500 mg/L was found, again indicating very low aquatic toxicity.

One key and one supporting study on the toxicity of DEHA to microorganisms are given in the ECHA Dissemination Portal. In the key 1996 study undertaken to EU Method C.11 under Directive 87/302/EEC, part C (Klimisch Score of 2), the 3 hour EC_{50} was >350 mg/L based on respiration rate. The supporting study conducted to DIN 38412, part 27 (Klimisch Score 2) gave 0.5 hour EC_{10} and EC_{20} values for *Pseudomonas putida* of >10,000 mg/L, the highest level tested.

Although there is no data on toxicity in sedimentary species, a study in the earthworm, *Eisenia fetida*, informs on terrestrial toxicity. In this study, conducted to EU Method C.8 under Directive 87/302/EEC, part C, p. 95, the LC_{100} value over 14 days of >1,000 mg/kg was reported.

[35] ASTM American Society for Testing and Materials, Philadelphia, PA, USA

4.7.3.2 Comparison of hazards

Table 4.51 compares DEHA to DBP in terms of DN(M)EL values. The Table is based on the information presented in the ECHA Dissemination Portal. This information should, however, be considered in the light of current uncertainty as to the appropriate interpretation of the experimental evidence on DEHA's reproductive toxicity.

Table 4.51: Human health risk comparison between DEHA and DBP

Parameter	DEHA		DBP	
Workers				
Acute / short-term exposure - systemic effects	Dermal DN(M)EL		Dermal DN(M)EL	
	Inhalation DN(M)EL		Inhalation DNEL	2.84 mg/m³
Acute / short-term exposure - local effects	Dermal DN(M)EL		Dermal DN(M)EL	
	Inhalation DN(M)EL		Inhalation DN(M)EL	
Long-term exposure - systemic effects	Dermal DNEL	25.5 mg/kg bw/day	Dermal DNEL	0.19 mg/kg bw/day
	Inhalation DNEL	17.8 mg/m³	Inhalation DNEL	0.13 mg/m³
Long-term exposure - local effects	Dermal DN(M)EL		Dermal DN(M)EL	
	Inhalation DN(M)EL		Inhalation DN(M)EL	
General population				
Acute / short-term exposure - systemic effects	Dermal DN(M)EL		Dermal DN(M)EL	
	Inhalation DN(M)EL		Inhalation DN(M)EL	
Acute / short-term exposure - local effects	Dermal DN(M)EL		Dermal DN(M)EL	
	Inhalation DN(M)EL		Inhalation DN(M)EL	
Long-term exposure - systemic effects	Dermal DNEL	13 mg/kg bw/day	Dermal DNEL	2.2 mg/kg bw/day
	Inhalation DNEL	4.4 mg/m³	Inhalation DNEL	0.62 mg/m³
	Oral DNEL	1.3 mg/kg bw/day	Oral DNEL	0.22 mg/kg bw/day
Long-term exposure - local effects	Dermal DN(M)EL		Dermal DN(M)EL	
	Inhalation DN(M)EL		Inhalation DN(M)EL	

Sources:
CSR
European Chemicals Agency: http://echa.europa.eu/
Note that for the general population, the CSR does not include toxicological thresholds, as consumer exposure is not considered relevant to the uses of the substance. The figures noted above in the grey part of the Table are from the registration of DBP, as shown on the ECHA Dissemination Portal

Table 4.52 compares the environmental hazard profile of DEHA with that of DBP, in terms of their proposed PNECs. The values for DBP are more stringent than those for DEHA with the exception of the freshwater aquatic PNEC for which DEHA's is lower than the PNEC for DBP.

Table 4.52: Environmental risk comparison between DEHA and DBP

Parameter	DEHA		DBP	
Aquatic organisms				
Freshwater	PNEC aqua (freshwater)	3.2 µg/L	PNEC aqua (freshwater)	10 µg/L
Marine water	PNEC aqua (marine water)	3.2 µg/L	PNEC aqua (marine water)	1 µg/L
Intermittent releases	PNEC aqua (intermittent releases)	3.2 µg/L	PNEC aqua (intermittent releases)	
STP	PNEC STP	35 mg/L	PNEC STP	0.22 mg/L
Sediment (freshwater)	PNEC sediment (freshwater)	15.6 mg/kg sediment dw	PNEC sediment (freshwater)	1.19 mg/kg sediment dw
Sediment (marine water)	PNEC sediment (marine water)		PNEC sediment (marine water)	0.119 mg/kg sediment dw
Air				
Air				No hazard
Terrestrial organisms				
Soil	PNEC soil	0.865 mg/kg soil dw	PNEC soil	0.05 mg/kg soil dw
Predators				
Secondary poisoning	PNEC oral		PNEC oral	1.33 mg/kg food
Sources: *CSR* *European Chemicals Agency: http://echa.europa.eu/*				

Finally, Table 4.53 provides a comparison of concerns arising from DBP and DEHA by human health and environmental endpoint.

Table 4.53: Comparison of DEHA and DBP against human health and environmental endpoints

Hazard endpoint	DEHA	DBP
Human health		
Irritancy	Skin, inhalation	
Repeat dose	Toxic	Toxic
STOT	Kidney, liver, ovary	Liver, kidney, testes
Reproductive toxicity	Toxic (uncertain)	1B (male fertility)
Developmental toxicity	Toxic (uncertain)	1B (males)
Carcinogenicity	Yes but suspected to operate via a rodent specific mechanism	Data are insufficient to determine the carcinogenic potential. No evidence of carcinogenicity is available. The CSR assumes that the substance is not a carcinogen
Environment		
Aquatic	Uncertain (conflicting evidence but also $PNEC_{freshwater}$ lower than DBP's)	Very toxic

Hazard endpoint	DEHA	DBP
Other		
Listing in the Community Rolling Action Plan (CoRAP)	DEHA is listed in the 2013-2015 CoRAP. The substance has been listed by Finland based, in part, on reproductive toxicity. The initial concerns are described as: *Human health/ Suspected CMR; Exposure/ Wide dispersive use; Consumer use; Aggregated tonnage* Expected year of Evaluation: 2015	
Note: grey cells indicate areas where no relevant information is available 2013-2015 CoRAP available at: http://echa.europa.eu/documents/10162/13628/corap_2013_en.pdf (accessed on 5 July 2013)		

Table 4.51 indicates that, overall, DEHA has been suggested to warrant the setting of higher DNELs for workers. On the other hand, Table 4.53 shows that there is some uncertainty with regard to the extent to which it may constitute a human health concern, particularly in relation to its reproductive and developmental toxicity. It is of note that the Finnish Authorities have added DEHA to the CoRAP in respect to its suspected CMR properties.

4.7.4 The available information on the ecotoxicity of DEHA clearly demonstrates that this substance does not constitute an environmental hazard even at aqueous concentration above its limit of solubility, indicating that there are no environmental concerns.Economic feasibility

DEHA can only be used in propellants as a plasticiser. Only <<10% of the tonnage of DBP currently used by the applicant's DUs is relevant to its role as a plasticiser. Therefore, the scope for sales of DEHA as a substitute for DBP in propellant formulation is very limited, particularly when considering that the plasticising effect of DEHA is considered worse than the effect of DBP. DEHA could not be used in the vast majority of small calibre ammunition, which accounts for the most important final products for DBP-based propellant mixtures.

Overall, although currently manufactured by the applicant, the substance cannot be considered economically feasible. Under a refused Authorisation, sales of DBP to propellant manufacturers would be lost and could only be replaced by a much more modest level of DEHA sales, if any at all. It must be noted that there are several other companies that have registered the substance and DEZA will not be the only supplier to place DEHA on the market.

Some additional detail is provided in the Confidential Annex.

Additional confidential information is presented in: AoA Confidential Annex DBP Propellants DEZA.pdf, Section 4.1.3

4.7.5 Availability

The substance is currently produced by DEZA in sufficient quantities (100-1,000 t/y). Several other registrants appear in ECHA's Dissemination Portal.

4.7.6 Conclusion on suitability and availability of DEHA

4.7.6.1 Technical suitability

The substance is available to the applicant and it is currently being manufactured, therefore it can be considered technically feasible from the applicant's perspective.

From the perspective of the DUs, DEHA is described as suitable only as an alternative plasticiser. This would mean that it is suitable to replace <<10% of the current tonnage of DBP consumed by propellant manufacturers within the applicant's supply chain. Moreover, even as a plasticiser DEHA is expected to perform worse than DBP and would require substantial re-formulation of the propellant products. Overall, the substance makes a poor substitute for DBP.

It must be noted however that DEHA has not been trialled by all propellant manufacturers and the assessment of its suitability varies among companies that have made an input to this analysis, due to their different requirements (i.e., their need for a moderant vs. the need for a plasticiser).

4.7.6.2 Reduction in overall risk

The DNEL values for DEHA in the ECHA Dissemination Portal are higher than the DNEL values for DPB in workers. However, DEHA shows some evidence of mammalian toxicity particularly in relation to concerns regarding its reproductive toxic. Such concerns would appear to be pertinent to the recent listing of DEHA on the CoRAP instigated in respect to its potential CMR properties.

On the other hand, the available information on the ecotoxicity of DEHA demonstrates that this substance does not constitute an environmental hazard even at aqueous concentration above its limit of solubility; yet, the $PNEC_{freshwater}$ value presented in the ECHA Dissemination Portal is lower than the respective value for DBP.

4.7.6.3 Economic feasibility

DEHA is currently manufactured by the applicant but cannot be considered economically feasible; only a very small tonnage of DEHA could be potentially sold as a substitute plasticiser for DBP in propellants, if any at all.

4.7.6.4 Availability

DEHA is available both to the applicant and their EU-based DUs.

Key point 15

DEHA is not a realistic alternative for the applicant. Although technically feasible and with a human health hazard profile generally more benign than DBP (but with some concerns over its repeat dose toxicity and rodent hepatic carcinogenicity), its economic feasibility is poor

g) ALTERNATIVE SUBSTANCE: ACETYL TRIBUTYL CITRATE

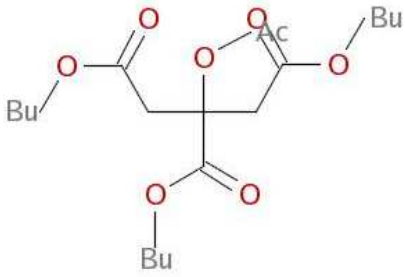
4.8 Acetyl tributyl citrate

4.8.1 Substance ID and properties

4.8.1.1 Name and other identifiers for the substance

The following Table presents the identity of ATBC.

Table 4.54: Identity of ATBC

Parameter	Value	Source
EC number	201-067-0	1
EC name	Tributyl O-acetylcitrate	1
CAS number	77-90-7	1
IUPAC name	Tributyl 2-acetoxypropane-1,2,3-tricarboxylate	4
Other names	1,2,3-propanetricarboxylic acid, 2- (acetyloxy)-, tributyl ester Citric acid, tributyl ester, acetate (8CI) Tributyl 2-acetylcitrate Citroflex A-4 CITROFOL BII	2
Molecular formula	$C_{20}H_{34}O_8$	1
SMILES notation	O=C(OCCCC)CC(OC(=O)C)(C(=O)OCCCC)CC(=O)OCCCC	2
Molecular weight	402.48	3
Molecular structure		1

Sources:
1: ESIS Internet site: http://esis.jrc.ec.europa.eu/
2: ChemSpider Internet site: http://www.chemspider.com/Chemical-Structure.6259.html
3: Chemical Book Internet site: http://www.chemicalbook.com/CASEN_77-90-7.htm
4: European Chemicals Agency: http://echa.europa.eu/
Important Note: information from the ECHA Dissemination Portal was obtained in late 2012. However, at the end of February 2013, the above link was no longer valid. Indeed the substance does not appear in the Registration database under the above EC number and the CAS number appears to be allocated to a different chemical substance (date of last search: 5 July 2013)

4.8.1.2 Composition of the substance

No information is available on constituents or impurities of the commercially available substance, including in the ECHA Dissemination Portal.

A quick search on the Internet can reveal several commercially available ATBC products with purity of 98% and above.

However, we note a particular notification of classification and labelling shown on the ECHA C&L Inventory[36]. Twelve companies notified the substance as a gas with a classification of Muta. 1B (H340) and Carc. 1B (H350), accompanied by Note K. Note K states that the classification as a carcinogen or mutagen need not apply if it can be shown that the substance contains less than 0.1% w/w 1,3-butadiene (EINECS No 203-450-8). If the substance is not classified as a carcinogen or mutagen, at least the precautionary statements (P102-)P210-P403 or the S-phrases (2-)9-16 should apply. Therefore, it is reasonable to assume that under certain circumstances ATBC may be accompanied by impurities (1,3-butadiene) which could lead to a Carc. 1B and Muta. 1B classification. This classification is not believed to be of direct relevance to the ATBC product that might be used by propellant manufacturers.

4.8.1.3 Physico-chemical properties

The following Table presents the key physico-chemical properties of ATBC. The information has been collected from the ECHA Dissemination Portal and other sources, including consultation with stakeholders.

Table 4.55: Physico-chemical properties of ATBC

Property	Value	Remarks	Source
Physical state at 20°C and 101.3 kPa	Colourless, slightly viscous liquid		1
Melting/freezing point	-57°C at 101.3 kPa		1
	-59°C		2
	-80°C or -75°C	Consultation response	
Boiling point	331°C at 97.64 kPa		1
	327°C		2
	173°C	Consultation response	
Density	1.0528 g/cm³ at 20°C		1
Vapour pressure	6.93 x 10^{-3} kPa at 20°C		3
	4.94 x 10^{-5} kPa at 25°C	EPISUITE 4.00 (MPBPVP v1.43), Modified Grain method	1
	6.1 x 10^{-7} kPa at 25°C		4
	0.11 kPa at 170°C		2
Surface tension	54.6 mN/m at 4 mg/L		1
Water solubility	4.49 mg/L at 20°C		1
	<100 mg/L		3
	2.045 mg/L	EPIWIN (v 3.10), WSKOWWIN Program (v 1.40)	3
Partition coefficient n-octanol/water	4.86at 40°C and pH 7.1		1
Flash point	217.9°C at 101.7 hPa		1
	204°C		2

[36] Available here: http://clp-inventory.echa.europa.eu/SummaryOfClassAndLabelling.aspx?SubstanceID=111970&HarmOnly=no?fc=true&lang=en date of last search: 5 July 2013).

Property	Value	Remarks	Source
Flammability	No data	Data waiving – study scientifically unjustified	
Explosive properties	No data	Data waiving – study scientifically unjustified	
Self-ignition temperature	No data		
Oxidising properties	No data	Data waiving – study scientifically unjustified	
Granulometry	No data	Data waiving – study scientifically unjustified	

Source:
1: European Chemicals Agency: http://echa.europa.eu/
2: ATBC Technical Datasheet, Vertellus Internet site:
http://www.vertellus.com/Documents%5CTechSheet%5CCITROFLEX%20A4%20English.pdf
3: US EPA Robust Summary and Test Plant: http://www.epa.gov/hpv/pubs/summaries/acetlcit/c15025rs.pdf
4: US Consumer Product Safety Commission: http://www.cpsc.gov/about/cpsia/phthalsub.pdf

4.8.1.4 Classification and labelling

A search in ECHA's C&L Inventory in 2012 suggested that no harmonised classification and labelling for ATBC is available. However, several notified classifications and labelling were identified. These are presented in Table 4.56. The Inventory suggested that the lead registrant and a further 1,285 notifiers did not classify the substance; a further 58 notifiers found the available data lacking.

Table 4.56: Notified classification and labelling of ATBC according to CLP criteria

Classification		Labelling		Number of Notifiers
Hazard Class and Category Code(s)	Hazard Statement Code(s)	Hazard Statement Code(s)	Pictograms Signal Word Code(s)	
Flam. Gas 1	H220	H220	GHS02 GHS08 GHS04 Dgr	12
Muta. 1B	H340	H340		
Carc. 1B	H350	H350		
Skin Irrit. 2	H315	H315	GHS07 Wng	3
Eye Irrit. 2	H319	H319		
Eye Irrit. 2	H319	H319	GHS07 Wng	3
Aquatic Chronic 3	H412	H412		1

Source:
European Chemicals Agency: http://echa.europa.eu/

4.8.1.5 REACH Registration details

The following Table summarises the available information on the status of REACH Registration for ATBC.

Table 4.57: REACH Registration status of ATBC

Registration	Result	Date of last search
Pre-registered	Yes	4 June 2012
Registered	Unknown - Originally found but searches on 27 February 2013 and 5 July 2013 did not reveal a registration entry	5 July 2013

Source:
European Chemicals Agency: http://echa.europa.eu/

4.8.2 Technical feasibility

4.8.2.1 Technical feasibility from the perspective of the applicant

DEZA does not currently manufacture this substance and does not have any current plans to start production in the future without a clear indication from its DUs that ATBC would be a technically feasible and acceptable alternative.

The Confidential Annex to this AoA explains that DEZA's ability to obtain the precursors to ATBC, which the company does not currently manufacture. Upon enquiry, the applicant has confirmed that they are not familiar with the conditions and parameters under which the manufacture of ATBC might be undertaken, and expects difficulties with implementing a manufacturing campaign for the substance, including concerns regarding purity.

Overall, the applicant cannot manufacture ATBC at present. Technically, this alternative cannot be considered feasible for the applicant at present.

Additional confidential information is presented in: AoA Confidential Annex DBP Propellants DEZA.pdf, Section 4.1.2

4.8.2.2 Technical feasibility from the perspective of downstream users

Relevance as substitute for DBP

According to consultation, the relevance of the substance as a substitute for DBP in propellant mixtures is as follows:

Substance family	Citrate esters
Function	Moderant and plasticiser (consultation also suggests a particular relevance as a coolant too)

Background to the use of the substance

Functions of ATBC in propellants: ATBC consists of citrate with three ester bonded butyl groups and one acetyl group bonded to the fourth available oxygen atom. Among other uses, ATBC is used as a non-VOC solvent in nitro-cellulose propellants (Bolgar & al, 2008) and it has been promoted as a substitute for DBP (Vertellus, 2012). ATBC may also be used as a non-energetic plasticiser in propellants for micro gas generators used in automotive seat pre-tensioners (Mangum, Emery, & Ryder, 2002).

Non-explosive uses of ATBC: ATBC is widely used as a plasticiser in food contact polymer applications. It is claimed to perform well as a plasticiser in vinyl toys for children offering excellent processing options, low toxicity, and a long history of use in sensitive applications. It provides improved adherence to metals, low volatility and resistance to yellowing. It is used in ink formulations, vinyl gloves, nail polishes, adhesives and coatings. Finally, it is effective in solution coating for both paperboard and foil (Vertellus, 2012).

Apart from PVC, resins to be plasticised with ATBC include cyanoacrylates (medical applications) and polylactides (surface coatings, films, coated papers, and mouldings) (Wypych, 2004).

Finally, ATBC is reported to be used as plasticisers in the production of cosmetics such as nail products (Johnson, 2002), aerosol hairsprays (Unitex, 2009b) and as a flavouring agent (WHO, 2000).

Comparison against key technical feasibility and selection criteria

Trials with the substance and perceived overall technical suitability: this information is presented in the Confidential Annex.

Comparison against the key technical feasibility and selection criteria: this information is presented in the Confidential Annex.

Additional confidential information is presented in: AoA Confidential Annex DBP Propellants DEZA.pdf, Section 4.8.2.2

4.8.3 Reduction of overall risk due to transition to the alternative

4.8.3.1 Hazard information

Mammalian hazard profile

This Section discusses the results of key and supporting studies from the ECHA Dissemination Portal, together with other sources, including the output from QSAR modelling where this was considered to provide relevant additional information. It should be noted that as of 5 July 2013 and since late February 2013, the Portal offered no access to the ATBC entry for unknown reasons.

Toxicokinetics: the ECHA Dissemination Portal summarised a robust (Klimisch Score 1) toxicokinetic study in Sprague-Dawley rats by Hiser *et al*. (1992) using the radiolabelled substance ([14^C]ATBC) given by oral gavage at a dosage of 70 mg/kg bw. This showed that ATBC was readily absorbed (>67% absorption, with t½ of 1.0 h), but was then rapidly and completely metabolised and excreted, with 9 metabolites being identified in urine (including acetyl citrate, mono-butyl citrate - tentatively the major metabolite, acetyl mono-butyl citrate, dibutyl citrate, and acetyl dibutyl citrate) and 3 in faeces. Urinary metabolites positively identified were acetyl citrate, mono-butyl citrate (tentatively the major metabolite), acetyl mono-butyl citrate, dibutyl citrate, and acetyl dibutyl citrate. After 24 hours, blood clearance was in excess of 87% of administered radioactivity, giving an elimination half-life (t½) of 3.4 hours. However, SCENIHR concluded that blood clearance was biphasic with half-lives of 3.9 and 39 hours (SCENIHR, 2008). One of the two supporting studies also reported, perhaps unsurprisingly, that ATBC was hydrolysed more slowly in human serum (t½ = ca. 7 h) than in rat liver homogenate (t½ = <30 min) but that the metabolites produced were similar.

Acute toxicity: the acute oral toxicity study in rats (Klimisch Score 2) at dosages of up to 31,500 mg/kg resulted in signs of gastrointestinal disturbance but no deaths over a 21 day observation period. The LD_{50} was estimated at >ca. 31,500 mg/kg. A supporting study in cats (Klimisch Score 2) reported signs suggestive of slight nausea and also diarrhoea for less than 24 hours following dosage of up to 50,000 mg/kg bw, but no deaths. No studies on inhalation toxicity were identified but an acute dermal toxicity study in male rabbits (Klimisch Score 2) in which ATBC was applied to intact skin for 4 days at ca. 1000 mg/kg resulted in no adverse effects.

Irritation and sensitisation: an unpublished non-guideline skin irritation study in rabbits (judged as Klimisch Score 2 by the notifiers but for which supporting methodological detail is apparently lacking), identified no evidence of dermal irritation at a dosage of ca. 1000 mg/kg. A further unpublished non-guideline study on ocular irritation in rabbits (again, reported as Klimisch Score 2) reports moderate erythema in 2/3 of rabbits in 20 minutes, persisting throughout the remainder of a 3 hour observation period, but the effect was only still apparent in one rabbit when observed after 5

and 24 hours. The effect in this animal had resolved within 48 hours. ATBC was therefore considered to be a slight eye irritant by the assessors.

Based on summary information included in a publicly available '*Notice of Filing a Pesticide Petition to Establish a Tolerance for a Certain Pesticide Chemical in or on Food*' to the US EPA (Klimisch Score 4), relating to a Draize repeat insult patch test in 59 human volunteers and in a Guinea pig maximisation test similar to OECD Guideline TG 406, a weight of evidence was advanced to justify a conclusion that ATBC was found not to induce dermal irritation or contact sensitisation. Support for this conclusion is also provided by the output of QSAR modelling (based on the TOPKAT system, see Table 4.58 overleaf) which indicates ATBC to be a non-sensitiser.

Repeat dose toxicity: the ECHA Dissemination Portal specifies only two studies as key, though several supporting studies that inform on the repeat dose toxicity of ATBC are also reported. In an apparently unpublished study in Wistar rats conducted according to OECD TG 408, but not to GLP (Klimisch Score 1), animals were fed diets containing ATBC so as to achieve dosages of 0, 96.02, 287.50 or 961.16 mg/kg bw/day over 13 weeks. Treatment-related changes comprised slight clinical chemistry perturbations (decreased globulin and bilirubin levels and aspartate aminotransferase and lactate dehydrogenase activities, and disturbed electrolyte profile) and at a high dosage a liver weight increase was noted, accompanied by post mortem observations of liver enlargement in two females and evidence of minimal hepatocellular hypertrophy at this dosage. The authors consider the changes to reflect metabolic adaptation, though no detailed argumentation to support this view (as opposed to regarding this as evidence of toxicity) is given. The authors thus suggest that the NOAEL should be regarded as 1000 mg/kg bw/day. In an apparently unpublished combined repeated dose and carcinogenicity dietary study in Wistar rats (reported as conducted to guidelines 875/318/EEC; 83/571/EEC; 91/507/EEC) (Klimisch Score 1), animals were fed a diet containing ATBC designed to achieve nominal dosages of 0, 100, 300, 1000 mg/kg bw/day for 12 months. No effects were reported on survival, clinical signs, at ophthalmoscopic examination, or in food consumption and haematological parameters. The liver was the target organ, with a NOAEL at 52 weeks of 300 mg/kg bw/day in males and 1000 mg/kg bw/d in females based on changes in body and liver weight and the occurrence of centrilobular hepatic hypertrophy. It should, however, be noted that several of the supporting studies also reported are assigned Klimisch Scores of 1 or 2, and some of these indicate that the NOAEL for repeat dose toxicity may be somewhat lower than the 300 mg/kg bw/day proposed by the registrant.

In addition, in a 90-day study in CD BR rats given ATBC at levels designed to achieve dosages of 0, 100, 300, or 1000 mg/kg bw/day via the diet, an increase in blood alkaline phosphatase (ALP) and a decrease in urinary pH was apparent in both sexes at 1000 mg/kg/d and in males at 300 mg/kg/day. An increase in body weight-relative to liver and kidney weights was also noted at 1,000 mg/kg bw/day. In another study, dietary administration to juvenile Han Wistar rats at up to 1,000 mg/kg bw/day for 13 weeks resulted in reduced body weight gain and hepatic enlargement at 1,000 mg/kg/day, while at 300 mg/kg/day few differences from controls were seen. Based on a review of these findings it was concluded that toxicological significance was only warranted to changes at the high dosage of 1000 mg/kg/d and suggested that the NOAEL for repeat dose toxicity should be considered to be 300 mg/kg/d (Hirata-Koizumi, Takahashi, Matsumoto, Kawamura, Ono, & Hirose, 2012). However, detailed argumentation to support this proposal was not adequately provided by the authors raising questions as to the robustness of such a conclusion.

Importantly, in their recent review, SCENIHR considered the findings of a 90-day rat study by oral gavage in which haematological and blood biochemical changes were noted at 300 mg/kg bw/day while at 1000 mg/kg bw/day liver weight increased (SCENIHR, 2008).

Table 4.58: Potential endocrine effects for ATBC

Hazard endpoint		Finding	Data source	Study design	Assessed robustness/Comment
Sensitisation	In vivo - Skin sensitisation	Non sensitiser	OECD QSAR	OECD QSAR prediction based on TOPKAT database for G*uinea pig Maximisation Test*	N/A
Protein binding potential		No alert found	OECD QSAR	QSAR prediction	No indication identified that model was operating outside of its operational limits
		No alert found	OASIS (in OECD QSAR)	QSAR prediction	No indication identified that model was operating outside of its operational limits
Androgen receptor binding activity		-2.73 to -10000 log RBA	FDA EKDB model	Model drew comparison with dibutyl adipate, di(2-ethylhexyl) adipate and di-i-butyl adipate	Model reports that on the basis of only limited similarity with compounds in database (0.47-0.48), no conclusion should be drawn
Oestrogen gene activation		-10000 log RP	FDA EKDB model	Model drew comparison with glycyrrhizic acid, 2K, dibutyl adipate and di(2-ethylhexyl) adipate	Model reports that on the basis of only limited similarity with compounds in database (0.48-0.49), no conclusion should be drawn
Oestrogen receptor binding activity (RBA)		RBA = 10%	OECD QSAR	QSAR prediction for oestrogen receptor binding activity (Multicase)	Reported to be outside of QSAR domain, hence considered of doubtful reliability
		-10000 log RBA	FDA EKDB model	Model drew comparison with di(2-ethylhexyl) adipate, bis(n-octyl) phthalate and Cineole	Model reports that on the basis of only limited similarity with compounds in database (0.32-0.48), no conclusion should be drawn

Sources:
OECD QSAR Data obtained using OECD QSAR Toolbox at Internet site:
http://www.oecd.org/chemicalsafety/assessmentofchemicals/theoecdqsartoolbox.htm#Download_qsar_application_toolbox
FDA EKDB data obtained using FDA EKDB Database at Internet site:
http://www.fda.gov/ScienceResearch/BioinformaticsTools/EndocrineDisruptorKnowledgebase/default.htm

More recently a report (Maag, Lassen, Brandt, Kjølholt, Molander, & Hagen Mikkelsen, 2010) considered the toxicity of ATBC and focused on a study in Wistar rats fed a diet of 100, 300 and 1,000 mg/kg/day. It formed part of a reproductive study in which F1 generation animals were treated for 13 weeks following exposure of the parent generation during pre- and post-mating periods, through to weaning (involving treatment of animals prior to mating and the pre- and post-natal period). They noted effects on body weight gain in both sexes and increased liver weight at the high dosage, together with signs of hepatic hypertrophy. Weak peroxisome proliferase activity was apparent in males at 300 mg/kg/day (a change of questionable human significance) and in both sexes at 1,000 mg/kg/day. Based on these results, a NOAEL in males of 100 mg/kg/day and of 300 for females was considered appropriate, and consequently, in the light of these authoritative reviews, it should be concluded that 100, rather than 300, mg/kg bw/day, should be regarded as the NOEL for this endpoint.

Genetic toxicity: the ECHA Dissemination Portal cites, for in vitro effects, a bacterial reverse mutagenicity study without inclusion of metabolic activation that was similar to OECD TG 471 in *S. typhimurium* (strains TA1535, TA1537, TA1538, TA98 and TA100) (Klimisch Score 2). No indication of mutagenic activity was found.

A series of other bacterial (Ames) or mammalian cell (mouse lymphoma, Chinese Hamster Ovary (CHO) and primary lymphocyte cell assays (Klimisch Scores 1 or 2) are also cited as supporting studies, all of which identified no evidence of mutagenic potential. In vivo, the key study identified is a mammalian bone marrow chromosome aberration assay (to OECD Guideline 475 and GLP; Klimisch Score 1) on Wistar rats given a single oral dose of 2000 mg/kg bw. No evidence for any chromosomal effect was identified. Further support is also given by a negative finding from an unscheduled DNA synthesis (UDS) test on liver from Han Wistar rats given dosages of 800 or 2000 mg/kg conducted to OECD TG486 (Klimisch Score 2). The conclusion that ATBC was not genotoxic was supported by additional reports (e.g. (SCENIHR, 2008), (Maag, Lassen, Brandt, Kjølholt, Molander, & Hagen Mikkelsen, 2010)).

Carcinogenicity: according to the ECHA Dissemination Portal, the key study on carcinogenicity was conducted to Guidelines 875/318/EEC; 83/571/EEC and 91/507/EEC and to GLP (Klimisch Score 1) and represents the carcinogenic study phase from the combined repeat dose and carcinogenicity study discussed above in relation to repeat dose toxicity. The substance is reported not to have elicited any treatment-related neoplastic change at dosages of up to1000 mg/kg bw/d. Although not included on the Dissemination Portal, SCENIHR (2008) comment on a two-year dietary study in rats in which no significant effects were identified. However, they provide little detail other than noting that the study was not to modern standards and that caution was needed in interpreting the findings.

Reproductive and developmental toxicity: the ECHA Dissemination Portal cited only two studies informing on the substance's reproductive toxicity, neither of which is indicated as being a key study for this endpoint. The first is an unpublished two-generation dietary study in an unspecified rat strain that is stated to comply with US EPA OPPTS 870.3100, OECD Method 408 and EC Method B26 guidelines and to GLP (Klimisch Score 1) and in which animals received dosages of 0, 100, 300 or 1000 mg/kg bw/day. No in-life or necropsy changes attributable to treatment are reported but the authors conclude that the NOAEL value for reproduction (and developmental) toxicity is 300 mg/kg/day for the F0 (parental) generation but 1000 mg/kg/day in the F1 (offspring) generation. However, given the lack of detailed information presented on the study findings, it is unclear as to why different NOAEL values were suggested to apply between the generations. In the second study, which was also a two-generation dietary investigation at the same dosages conducted in a manner similar to OECD Guideline 416 but with only limited histophathological examination (hence judged Klimisch Score 2), findings are poorly reported and

it is not possible to assess the robustness of the authors' conclusion that the NOAEL for the F0 and F1 generation was only 100 mg/kg bw/day.

SCENIHR (2008) also discuss two multi-generation studies using the same dosages, but given the absence of definitive reference citations, it is not possible to confirm absolutely if these are identical or not to those cited in the Dissemination Portal. In their review, SCENIHR comment that in one study no effects of ATBC were identified in any reproductive endpoints and offspring survival and growth and endocrine systems were unaffected, whilst in the second study dosages of 300 mg/kg/d or above produced only bodyweight effects, such that the study NOEL was considered to be 100 mg/kg bw/day. Overall, therefore, it may be assumed that while there is evidence of material repeat dose toxicity at dosages in excess of 100 mg/kg bw/day, there is no evidence of ATBC affecting reproductive endpoints at up to 300 mg/kg bw/day.

The ECHA Dissemination Portal cited as the key study one on rats. Although stated as not being conducted to an established guideline or GLP and to lack detail in reporting, it is reported to warrant a Klimisch Score of 2. In the study, rats of unspecified strain were apparently given feed containing a milk solution of ATBC at 0, 50 or 250 mg/kg for 12 months. After 9 months, animals were mated and male gonads and embryotoxicity (numbers of corpora lutea, implantation sites, resorptions and deformities) and offspring development (birth length, ear and eye opening, appearance of body hair and teeth, behaviour and body weight) were examined. The maternal NOAEL is stated as 50 mg/kg, while the NOAEL for developmental toxicity is 250 mg/kg bw/d. A similarly constituted study in mice from the same paper, which showed a similar picture, is presented as a supplementary entry. Additional details are provided in a submission to the US EPA prepared by Toxicology/Regulatory Services, Inc. (2003), in which it is reported that, while still considering the study to have a developmental NOAEL of 250 mg/kg bw/d, there were increases in body weight and length of the offspring and in placental weights at the 250 mg/kg bw/day dosage. Further reassurance as to the validity of the 250 mg/kg dosage as the NOAEL for ATBC is, however, provided by the lack of apparent developmental effects even at high dosages in the two-generation studies discussed above.

Other toxicities: SCENIHR (2008) note that multi-generation studies have not suggested any endocrine disruptor potential for ATBC but it is not clearly stated which endocrine-relevant endpoints had been considered. Therefore, QSAR modelling for its ability to interact with proteins and the oestrogen or androgen system were attempted but failed to establish robust predictions (see Table 4.58).

Although not mentioned in either the ECHA Dissemination Portal or by SCENIHR (2008), Maag *et al*. (2010) report that ATBC has elicited neurotoxic effects attributable to local anaesthetic/neural blockade when applied in a 3% acacia to the sciatic nerve of rats and in a 5% suspension of ATBC in 3% gum acacia to the conjunctival sac of the eye of a rabbit. However, given the lack of overt signs of neurotoxicity reported in either the repeat dose or reproductive/developmental studies considered above, it may be concluded that the reported changes should not be regarded to be of significant concern.

<u>Environmental fate and behaviour and ecotoxicology</u>

The ECHA Dissemination Portal provided information on the environmental fate and bioaccumulation potential of ATBC. A biodegradation test similar to OECD TG 302C indicated that 82% degradation occurred over 28 days, which would be suggestive of inherent biodegradability. This is not, however, supported by a finding of only 16% biodegradation (i.e. not readily biodegradable) in an EU Method C.4-E and OECD TG 301D compliant study. The SRC BIODEG database (see Table 4.59) includes a finding of 48-51% aerobic degradation in sewage for

a 28-day MITI test. Nonetheless, it is of note that the studies which are considered key studies concluded that ATBC is readily biodegradable in a range of media. A bioconcentration factor (BCF) of 31.57 L/kg wet wt (based on a measured logK_{ow} of 4.86) for ATBC, calculated using EPIWIN (v 4.0), BCFBAF Program (v 3.00) and considered to warrant a Klimisch Score of 2, is also derived leading to a conclusion that there is a low potential for bioconcentration. Furthermore, in a OECD TG 121 study (Klimisch Score 1), a log K_{oc} of 4.271 was determined using a HPLC method while Mackay Level I modelling of environmental distribution (Klimisch Score 2) showed that the substance was about equally distributed to air (27.8%), water (18.1%), soil (28.0%) and sediment (26.1%) with distribution to other compartments being negligible.

Overall, these findings, which are in line with the notified classifications for the substance, suggest that there should be little concern with regard to either the environmental fate and behaviour of ATBC or its bioaccumulation potential. However, some caution in uncritically accepting these conclusions may be warranted in the light of the findings of Maag *et al*. (2010) which report a calculated BCF of 250 and a K_{oc} of 1,800 based on a water solubility of 5 mg/L. On the basis of their findings, Maag et al. (2010) suggest ATBC may show some bioaccumulation potential as well as strong sorption properties (i.e. low mobility in soil). Detailed studies may be necessary to resolve these apparent conflicting opinions on its properties.

Table 4.59: Biodegradation information on ATBC from the SRC BIODEG database

Aerobic tests		**Anaerobic tests**	
Screening Test	BSA - 2	Anaerobic - Soil	-
Biological Treatment Simulation	BFA - 3	Anaerobic - Water	-
Grab Sample - Soil	BFA - 2	Anaerobic Summary	-
Grab Sample - Water	-	**Other**	
Field Test	-	Pure Culture	
Aerobic Summary	BST - 2	Number of References	2

Source:
SRC BIODEG Internet site: *http://srcinc.com/what-we-do/databaseforms.aspx?id=383*
Notes:
BF - Biodegrades fast
BFA - Biodegrades fast w/acclimation
BS - Biodegrades slow
BSA - Biodegrades slow w/acclimation
1 - Chemical tested in three or more tests, consistent results
2 - Chemical tested in two tests, or results in more than two tests are interpretable, but conflicting data
3 - Only one test or uninterpretable, conflicting data

With regard to the aquatic toxicological potential of ATBC, the key acute fish study identified is a 1974 flow-through 96-hour study of a design similar to OECD TG 203 (Klimisch Score 2) in Bluegill sunfish which gave a $LC_{50\ (96h)}$ of 38-60 mg/L (nominal) and a NOEC of 10 mg/L (nominal). These values are not dissimilar to that quoted as supplementary information for the marine species *Fundalus heteroclitus* of LC_{50}(96h) of 59 mg/L (nominal) and a NOEC of 10 mg/L (nominal) while, for invertebrates the key OECD TG202 study in Daphnids (Klimisch Score 2) reports a mobility EC_{50} (24 h) of >1mg/L. Algael toxicity, as assessed in a study compliant with EU Method C.3 and OECD TG 201 (Klimisch Score 1), gave 72h NOEC and LOEC values for growth of 4.65 and 10.9 mg/L respectively, equating to an EC_{50} of 74.4 mg/L. When yield was considered, the EC_{50} was lower at 11.5 mg/L. It should be noted, however, that Maag *et al*. (2010) make reference, amongst other generally more conservative estimates, to an acute study in fish in which the most sensitive finding was for *Pimephales promelas* larvae over 18 hr in a 7-day static-

renewal test to US EPA Method 1000.0, which indicated lower values (LC_{50} (48h) = 2.8 mg/L and LC_{50} (168hr) = 1.9 mg/L). Information about ATBC's long-term aquatic toxicity from the ECHA Dissemination Portal is restricted to a study using EU Method C.20 on *D. magna* (Klimisch Score 1) that reported a 21-day NOEC of ≥1.11 mg/L for reproduction rate and survival of adults. An EC_{50} (reproduction rate) of >1.11 mg/L was also quoted. It is possible that if reference was made to the studies noted by Maag et al. (2010), this might explain the inclusion of Aquatic Chronic 3-H412 categorisation by one of the notifiers of the substance.

4.8.3.2 Comparison of Hazards

Table 4.60 compares ATBC to DBP in terms of DN(M)EL values. The DNEL values for ATBC are from the ECHA Dissemination Portal.

Table 4.60: Human health risk comparison between ATBC and DBP

Parameter	ATBC		DBP	
Workers				
Acute / short-term exposure - systemic effects	Dermal DN(M)EL		Dermal DN(M)EL	
	Inhalation DN(M)EL		Inhalation DNEL	2.84 mg/m³
Acute / short-term exposure - local effects	Dermal DN(M)EL		Dermal DN(M)EL	
	Inhalation DN(M)EL		Inhalation DN(M)EL	
Long-term exposure - systemic effects	Dermal DNEL	2 mg/kg bw/day	Dermal DNEL	0.19 mg/kg bw/day
	Inhalation DNEL	7.04 mg/m³	Inhalation DNEL	0.13 mg/m³
Long-term exposure - local effects	Dermal DN(M)EL		Dermal DN(M)EL	
	Inhalation DN(M)EL		Inhalation DN(M)EL	
General population				
Acute / short-term exposure - systemic effects	Dermal DN(M)EL		Dermal DN(M)EL	
	Inhalation DN(M)EL		Inhalation DN(M)EL	
Acute / short-term exposure - local effects	Dermal DN(M)EL		Dermal DN(M)EL	
	Inhalation DN(M)EL		Inhalation DN(M)EL	
Long-term exposure - systemic effects	Dermal DNEL	1 mg/kg bw/day	Dermal DNEL	2.2 mg/kg bw/day
	Inhalation DNEL	1.74 mg/m³	Inhalation DNEL	0.62 mg/m³
	Oral DNEL	1 mg/kg bw/day	Oral DNEL	0.22 mg/kg bw/day
Long-term exposure - local effects	Dermal DN(M)EL		Dermal DN(M)EL	
	Inhalation DN(M)EL		Inhalation DN(M)EL	

Sources:
CSR
European Chemicals Agency: http://echa.europa.eu/
Important Note: the above information on ATBC appears to have been removed from the ECHA Dissemination Portal (date of last search: 5 July 2013, last accessed in late February 2013)
Note that for the general population, the CSR does not include toxicological thresholds, as consumer exposure is not considered relevant to the uses of the substance. The figures noted above in the grey part of the Table are from the registration of DBP, as shown on the ECHA Dissemination Portal

Due to the apparent removal of the ATBC entry from the ECHA Dissemination Portal a comparison of environmental PNEC values cannot be given in tabular form here.

Finally, Table 4.61 provides a comparison of concerns arising from DBP and ATBC by human health and environmental endpoints.

Table 4.61: Comparison of ATBC and DBP against human health and environmental endpoints

Hazard endpoint	ATBC	DBP
Human health		
Irritancy	Slight (eye)	
Repeat dose	Toxic	Toxic
STOT	Liver, kidney	Liver, kidney, testes
Reproductive toxicity		1B (male fertility)
Developmental toxicity		1B (males)
Carcinogenicity		Data are insufficient to determine the carcinogenic potential. No evidence of carcinogenicity is available. The CSR assumes that the substance is not a carcinogen
Environment		
Aquatic	Uncertain	Very toxic
Note: grey cells indicate areas where no relevant information is available		

Table 4.60 indicates that, compared to DBP, ATBC has a less severe DNEL established for systemic effects on workers under long-term exposure conditions via the inhalation and dermal route. However, a review of the available literature does raise some concerns as regards the conclusions reached by the registrant for the substance. More specifically, as discussed above, in the case of repeat dose toxicity, findings from some of the supporting studies (with Klimisch Scores of 1 or 2) reported by the registrants together with the conclusions drawn by SCENIHR (2008) and Maag *et al*. (2010) indicate that the NOAEL for repeat dose toxicity should probably be established at 100 mg/kg bw/day, rather than the 300 mg/kg bw/day indicated by the registrant.

Overall however, examination of the available information on the mammalian hazard data for ATBC identifies few concerns. As concluded by SCHENIR (2008), ATBC is not mutagenic or carcinogenic, has low acute toxicity, shows no significant evidence of reproductive or development effects at dosages of up to 300 mg/kg bw/d, and only elicits effects when given repeatedly at dosages in excess of 100 mg/kg bw/d (possibly as a result of having mild peroxisome proliferative properties).

With regard to its environmental effects, information as presented in the past on the ECHA Dissemination Portal indicates very little basis for concern, though it should be noted that Maag *et al*. (2010) have recently raised some concerns with regard to its potential to show aquatic toxicity and at least limited bioaccumulation potential although it is likely that detailed studies would be necessary to resolve this issue.

4.8.4 Economic feasibility

DEZA does not manufacture ATBC as it is unfamiliar with the technology and process parameters required for its production but, primarily, due to a lack of demand for the substance by the DUs.

Importantly, due to the unproven technical feasibility of the substance from the perspective of DUs, it is unclear whether any of them would actually use ATBC as a substitute of DBP. Moreover, even if ATBC would prove to be technically feasible for the applicant's customers, the volume of current sales of DBP to propellant manufacturers that could be substituted with ATBC would likely only be very modest, due to (a) the presence of other established suppliers (see Table 4.62) and (b) the overall small tonnage of moderant/plasticiser that is required in the "Applied for" Use.

It must be noted that a certain minimum tonnage of ester has to be manufactured before the economics of production become viable; the volume of current sales of DBP to propellant manufacturers cannot justify the investment cost associated with the setting up of a new production line for ATBC, especially since DEZA would face strong competition from established suppliers of the substance.

This alternative substance cannot be considered economically feasible for the applicant.

Additional confidential information is presented in: AoA Confidential Annex DBP Propellants DEZA.pdf, Section 4.1.3

4.8.5 Availability

4.8.5.1 Current and projected availability

Availability for the applicant

As discussed above, ATBC is manufactured using technology that is unknown to DEZA and its compatibility with the current esterification plant is uncertain. The applicant cannot manufacture ATBC at present.

Availability for the downstream users

From the perspective of the DUs, the market availability of ATBC is given in Table 4.62.

Table 4.62: Market availability of ATBC

Alternative	Data availability	Market availability from the perspective of the downstream users
ATBC	Very limited	Available on the market Unclear REACH registration status

4.8.5.2 Actions required for improving availability

Availability for the applicant

For ATBC to become available to the applicant the ability of the existing esterification plant to manufacture ATBC at sufficient quantities and in the required quality needs to be investigated, if there a market incentive for doing so.

The Confidential Annex to this AoA explains the tasks that the applicant would have to undertake in researching, trialling and starting the production of ATBC at their plant. The time that would be required for such production to be initiated at the industrial scale would extend beyond the Sunset Date for the Authorisation of DBP even if DEZA started the process of researching the production of ATBC as soon as this AfA was submitted.

The conclusion is that without a breakthrough in the DUs' R&D efforts, the availability of the substance for the applicant would be unlikely to improve in the foreseeable future.

Additional confidential information is presented in: AoA Confidential Annex DBP Propellants DEZA.pdf, Section 4.1.4

Availability for the downstream users

ATBC is generally available on the market for use by propellant manufacturers.

4.8.6 Conclusion on suitability and availability for ATBC

4.8.6.1 Technical suitability

The substance is not available to the applicant and it is manufactured with technology that is not currently known to them and may be incompatible with their existing facilities, therefore it may not be considered technically feasible.

From the perspective of the DUs, ATBC is described as suitable for consideration both as an alternative surface moderant and an alternative plasticiser. When ATBC is compared to DBP against the key technical feasibility and selection criteria, ATBC appears to have, in principle, small differences to DBP, as discussed in the Confidential Annex, but is likely to be suitable for use under current production processes for certain calibres only. The Confidential Annex explains that the theoretical use of the substance would require changes to production processes and reformulation in order to ensure that the propellant mixtures behave in a manner similar to existing DBP-based formulations.

4.8.6.2 Reduction of overall risk

With regard to ATBC human health and environmental hazard profile, the information available suggests that ATBC may pose a lower long-term hazard to human health compared to DBP. With regard to its environmental effects, information available indicates little basis for concern, though it should be noted that recent research has raised some concerns with regard to ATBC's potential to show aquatic toxicity and at least limited bioaccumulation potential, an issue which would require additional study to resolve.

As the risks from exposure to DBP from its use in the formulation and subsequent use of propellants are adequately controlled, the use of ATBC would not result in discernible benefits to DUs' workers' health.

4.8.6.3 Economic feasibility

Given the uncertain uptake of ATBC by DUs, the applicant's lack of knowledge over the production conditions and the need to ensure that a minimum sales tonnage must be achieved before the production of a new ester compound can be profitable, ATBC cannot be considered economically feasible for the applicant. This is particularly true because DEZA would have to compete against established suppliers of the substance.

4.8.6.4 Availability

From the perspective of the applicant, the substance is not available as its manufacture is based on technology unavailable to him. Moreover, the future availability of the substance is unlikely to

change; the quantity of ATBC that would be sold by DEZA is too small to justify the expense of setting up and operating a new production line based on unknown technology.

Key point 16

ATBC is an alternative substance that could theoretically be considered both as an alternative moderant and an alternative plasticiser. However, the technical feasibility of ATBC for DEZA is poor and the economics of production are unfavourable, although the hazard profile of the substance is apparently more benign than DBP's

h) ALTERNATIVE SUBSTANCE: TRIBUTYL CITRATE

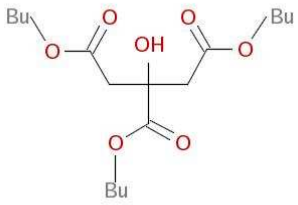
4.9 Tributyl citrate

4.9.1 Substance ID and properties

4.9.1.1 Name and other identifiers for the substance

The following Table presents the identity of TBC.

Table 4.63: Identity of TBC

Parameter	Value	Source
EC number	201-071-2	1
EC name	Tributyl citrate	1
CAS number	77-94-1	1
IUPAC name	Tributyl 2-hydroxy-1,2,3-propanetricarboxylate	2
Other names	Butyl citrate Citric acid, tributyl ester Dibutyl 3-(butoxycarbonyl)-3-hydroxypentane-1,5-dioate Tri-n-butyl citrate Citroflex 4 1,2,3-propanetricarboxylic acid, 2-hydroxy-, 1,2,3-tributyl ester Tributyl 2-hydroxypropane-1,2,3-tricarboxylate 1,2,3-tributyl 2-hydroxypropane-1,2,3-tricarboxylate 2-Hydroxy-1,3-propanetricarboxylic acid, tributyl ester 1,2,3-Propanetricarboxylic acid, 2-hydroxy-, 1,2,3-tributyl ester	2, 3, 4, 5
Molecular formula	$C_{18}H_{32}O_7$	1
SMILES notation	O=C(OCCCC)CC(O)(C(=O)OCCCC)CC(=O)OCCCC	2
Molecular weight	360.4	2
Molecular structure		1

Sources:
1: ESIS Internet site: http://esis.jrc.ec.europa.eu/
2: ChemSpider Internet site: http://www.chemspider.com/Chemical-Structure.6261.html?rid=7f1dba40-d7a9-4767-b127-eec6ae32da73
3: Chemical Book Internet site: http://www.chemicalbook.com/CASEN_77-94-1.htm
4: US EPA Internet site: http://ofmpub.epa.gov/sor_internet/registry/substreg/searchandretrieve/advancedsearch/externalSearch.do?p_type=SRSITN&p_value=6791
5: PubChem Compound Internet site: http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=6507

4.9.1.2 Composition of the substance

No information is available on constituents and impurities. The substance is registered as being available at between 100 and 1000 t/y on ECHA's database of registered substances[37].

4.9.1.3 Physico-chemical properties

The following Table summarises the available information on the physico-chemical properties of TBC. The information has been collected from a number of literature sources.

Table 4.64: Physico-chemical properties of TBC

Property	Value	Remarks	Source
Physical state at 20°C and 101.3 kPa	Clear, oily liquid		2
	Liquid		4
Melting/freezing point	-62°C		3
Boiling point	325°C		1
	≥309°C	Quoted from unpublished study to OECD Guideline 103	4
Density	1.042		2
	1.0432-1.0451	Quoted from unpublished study to EU Method A.3	4
Vapour pressure	1.00 mm Hg at 170°C		2
	2.48E-7 mm Hg at 25°C	Predicted with MPBPWIN v1.42 (Modified Grain method)	1
	0.0000756 mm Hg at 25°C	Predicted with MPBPWIN program v1.43.(Modified Grain method)	4
Surface tension	39.09 dyne/cm	ACD/PhysChem Suite	1
Water solubility	27.37 mg/L at 25°C	Estimate from $LogK_{ow}$ (WSKOW v1.41)	1
	48.548 mg/L	Estimate from Fragments Wat Sol (v1.01)	1
	102.7 mg/L at 20°C and pH 6.8	Quoted from unpublished study to EU Method A.6	4
Partition coefficient n-octanol/water	3.28	Predicted with KOWWIN v1.67	1
	3.5	Quoted from unpublished study to EU Method A.8	4
Flash point	157°C	Closed cup	3
	185°C	Cleveland open cup	2
	206.5 °C	Quoted from unpublished study to EU Method A.9	4
Flammability	No data		
Explosive properties	No data		
Self-ignition temperature	368°C		2
	360°C	Quoted from unpublished study to EU Method A.15	4
Oxidising properties	No data		

[37] Date of last search: 25 June 2013.

Property	Value	Remarks	Source
Granulometry	No data		
Sources: *1: ChemSpider Internet site: http://www.chemspider.com/Chemical-Structure.6261.html?rid=7f1dba40-d7a9-4767-b127-eec6ae32da73* *2: Vertellus MSDS: http://www.vertellus.com/Documents%5CMSDS%5CCitroflex%204%20English.pdf* *3: Science Lab MSDS: http://www.sciencelab.com/msds.php?msdsId=9925302* *4: European Chemicals Agency: http://echa.europa.eu/*			

4.9.1.4 Classification and labelling

No information on harmonised classification and labelling for TBC is available. However, ECHA's C&L Inventory identifies several aggregated notifications[38]. These are presented in Table 4.65. A further 131 notifiers did not classify the substance; the Registrant on the ECHA Dissemination Portal also did not classify the substance.

Table 4.65: Notified classification and labelling of TBC according to CLP criteria

Classification		Labelling		Number of Notifiers
Hazard Class and Category Code(s)	**Hazard Statement Code(s)**	**Hazard Statement Code(s)**	**Pictograms Signal Word Code(s)**	
Eye Dam. 1	H318	H318	GHS05 Dgr	93
Aquatic Acute 1	H400	H400	GHS09 Wng	43
Source: *European Chemicals Agency: http://echa.europa.eu/*				

4.9.1.5 REACH Registration details

The following Table summarises the available information on the status of REACH Registration for TBC.

Table 4.66: REACH Registration status of TBC

Registration	Result	Date of last search
Pre-registered	Yes	4 June 2012
Registered	Yes – 100-1,000 t/y	25 June 2013
Source: *European Chemicals Agency: http://echa.europa.eu/*		

4.9.2 Technical feasibility

4.9.2.1 Technical feasibility from the perspective of the applicant

DEZA does not currently manufacture this substance and does not have any current plans to start production in the future without a clear indication from its DUs that TBC would be a technically feasible and acceptable alternative.

[38] Date of last search: 5 July 2013.

The Confidential Annex to this AoA explains that DEZA's ability to obtain the precursors to TBC, which the company does not currently manufacture, and the possibilities of using the existing plant for the manufacture of this citrate.

DEZA has experience in esterification reactions and the manufacture of TBC would involve an esterification reaction with raw materials different to those of DBP. Upon enquiry, the applicant has confirmed that they are not familiar with the conditions and parameters under which the manufacture of TBC might be undertaken.

Overall, the applicant cannot manufacture TBC at present; the manufacture of TBC at DEZA's esterification plant is only a theoretical possibility. Technically, this alternative cannot be considered feasible for the applicant at present.

Additional confidential information is presented in: AoA Confidential Annex DBP Propellants DEZA.pdf, Section 4.1.2

4.9.2.2 Technical feasibility from the perspective of downstream users

Relevance as substitute for DBP

According to consultation, the relevance of the substance as a substitute for DBP in propellant mixtures is as follows:

Substance family	Citrate esters
Function	Moderant and plasticiser

Background to the use of the substance

Functions of TBC in propellants: information is available in the literature on its possible uses as a substitute for DBP in composite modified double-based propellants (Wang & al, 2010) and in propellants for automotive air bag inflators (Mangum, Emery, & Ryder, 2002). Information specific to its potential role in the products concerned by this AoA has not been retrieved.

Non-explosive uses of TBC: TBC is most commonly used as a solvent and plasticiser for polymers (particularly PVC). As a plasticiser, TBC is used in food contact materials, medical and pharmaceutical applications, toys, cigarette filters, cosmetics, lacquers and fragrances. It is also a component of adhesives based on acetate/acrylates, etc. (Chemicalland 21, undated-b) (Indo-Nippon Chemical Co, undated). Apart from PVC, resins to be plasticised with TBC include cellulose acetate (osmotic membranes), cyanoacrylates (medical applications), polylactides (films, coated papers, and mouldings), polyvinylacetate (sand/soil stabilisation) and methacrylate copolymers (automotive applications) (Wypych, 2004).

Comparison against key technical feasibility and selection criteria

Trials with the substance and perceived overall technical suitability: this information is presented in the Confidential Annex.

Comparison against the key technical feasibility and selection criteria: this information is presented in the Confidential Annex.

Additional confidential information is presented in: AoA Confidential Annex DBP Propellants DEZA.pdf, Section 4.9.2.2

4.9.3 Reduction of overall risk due to transition to the alternative

4.9.3.1 Hazard information

Information on the mammalian and environmental hazard potential of TBC is included in the ECHA Dissemination Portal; there are very few other sources of published information available. The available hazard data from non-ECHA sources is summarised in Table 4.67 below.

Table 4.67: Hazard information on TBC

Database/Source	Parameter	Value
German Federal Environmental Agency List of Substances which are Hazardous to Water	Hazard class (Note: there are three water hazard classes (WGK): 1: low hazard to waters 2: hazard to waters 3: severe hazard to waters)	1
Toxicity Journal of Pharmaceutical Sciences. Vol. 53, Pg. 774, 1964	Effect behavioural: somnolence (general depressed activity) vascular: other changes	LD_{50} = 2,900 mg/kg (mouse)
(USP, 2009)	Toxicity to animals (oral)	Rat LD_{50}: >30 mL/kg; 31.4 g/kg Cat LD_{50}: >50 mL/kg
(ClearSynth, undated)	Toxicity to animals (oral)	Mouse LD_{50} = 300 mg/kg Rabbit LD_{50} = 3,200 mg/kg Rat LD_{50} = 980 mg/kg
(Finkelstein & Gold, Toxicology of the Citric Acid Esters: Tributyl Citrate, Acetyl Tributyl Citrate, Triethyl Citrate, and Acetyl Triethyl Citrate, 1959)	Toxicity through the oral route in the rat and cat	Non-toxic, no gastrointestinal irritation or systemic effects in large single doses as high as those corresponding to more than 3L for a man of average weight. TBC proved inactive also when mixed with the diet and fed for 2 months in daily amounts as high as those corresponding to 1.4L daily for a man of average weight. This inactivity might be due to TBC's insolubility, which may interfere with absorption
US Army Military exposure guidelines (MEGs) for Short-Term exposures to chemicals in ambient air	1 hour Critical Air MEG	1.3×10^3 mg/m^3
	1 hour Marginal Air MEG	3.5×10^2 mg/m^3
	1 hour Negligible air MEG	50 mg/m^3
Food Safety	EPA Inert Ingredients	Listed 40 CFR Part 180
	FDA Cumulative Estimated Daily Intake (CEDI)/Acceptable Daily Intake Database	3.5×10^{-4} mg/kg bw/d Cumulative dietary concentration: 7.0 ppb
Sources: *German Federal Environmental Agency Internet site:* *http://webrigoletto.uba.de/rigoletto/public/searchDetail.do?kennummer=2213* *US EPA ACToR Internet site: http://actor.epa.gov/actor/GenericChemical?casrn=77-94-1*		

The limited data available on TBC are further supplemented by information generated by QSAR models (OECD QSAR toolbox and FDA EKDB models) so as to provide additional insight into the mammalian and ecotoxicological profile of this substance. The outputs of the modelling (and associated references) are presented in Table 4.68, overleaf. Based on all available information, the hazard profile of this substance may be summarised as follows.

Table 4.68: Human health and environmental hazard profile for TBC

Hazard endpoint		Finding	Data source	Study design	Assessed robustness/Comment
Toxicokinetics		83.3%	OECD QSAR	QSAR prediction of human intestinal absorption by Multicase expert system	Result reported to be undefined with regard to domain applicability; hence considered of doubtful reliability
Irritation	Skin irritation/corrosion	Negative	OECD QSAR	QSAR prediction by skin sensitisation, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Not irritating or corrosive to skin	OECD QSAR	QSAR prediction by (Bundesinstitut für Risikobewertung) BfR skin irritation/corrosion (for severe skin irritation)	Result reported to be undefined with regard to domain applicability; hence considered of doubtful reliability
		Not irritating or corrosive to skin	OECD QSAR	QSAR prediction by (Bundesinstitut für Risikobewertung) BfR skin irritation/corrosion (undefined endpoint)	Result reported to be undefined with regard to domain applicability; hence considered of doubtful reliability
		Negative	OECD QSAR	QSAR prediction by Severe skin irritation, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
	Eye irritation	Unknown	OECD QSAR	QSAR prediction by BfR eye irritation/corrosion	Result reported to be undefined with regard to domain applicability; hence considered of doubtful reliability
Sensitisation	In vivo - Skin sensitisation	Not sensitising	OECD QSAR	QSAR prediction by skin sensitisation, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
Genetic toxicity	In vitro - Mutagenicity	Negative	OECD QSAR	TWO QSAR predictions for Ames test (*S. typhimurium*))without information on metabolic status, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Negative	OECD QSAR	QSAR prediction for Ames test (*S. typhimurium*) with SP mix, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Negative	OECD QSAR	QSAR prediction for Ames test (*S. typhimurium*) without SP mix, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Positive	OECD QSAR	QSAR prediction for unscheduled DMA damage in rat cells, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Negative	OECD QSAR	QSAR prediction by DNA reactivity (based on DNA reactivity assay using Ashby fragments, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable

Hazard endpoint		Finding	Data source	Study design	Assessed robustness/Comment
		Negative	OECD QSAR	QSAR prediction by Ames test (Salmonella), from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Negative	OECD QSAR	QSAR prediction for HGPRT assay for mouse bone marrow cells, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
	In vitro – Chromosomal effect	Negative	OECD QSAR	QSAR prediction for sister chromosome exchange assay in Syrian Haster Embryo (SHE) cells, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Equivocal	OECD QSAR	QSAR prediction for chromosome aberration in Chinese hamster ovary (CHO) cells, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
	In vivo- Mutagenic effects	Negative	OECD QSAR	QSAR prediction for a Drosophila sex-linked recessive lethal assay, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
	In vivo – Chromosomal effect	Negative	OECD QSAR	QSAR prediction for mouse micronucleus assay, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
Carcinogenicity		Negative	OECD QSAR	QSAR prediction for FDA Cancer Female Mouse, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Negative	OECD QSAR	QSAR prediction based for FDA Cancer Male Mouse, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		TD_{50} = 1000 mg/kg/day	OECD QSAR	QSAR prediction from mouse Carcinogenic Potency Database (CPDB), from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Negative	OECD QSAR	QSAR prediction for FDA Cancer Female Rat, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Negative	OECD QSAR	QSAR prediction for FDA Cancer Male Rat, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		TD_{50}= 1000 mg/kg/day	OECD QSAR	QSAR prediction from rat Carcinogenic Potency Database (CPDB), from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
Toxicity to reproduction	Reproductive	No information			
Developmental toxicity / Teratogenicity		Negative	OECD QSAR	QSAR prediction based on FDA Teratogen Information System (TERIS), from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable

Hazard endpoint		Finding	Data source	Study design	Assessed robustness/Comment
Other toxic endpoints	Protein binding potential	No alert found	OECD QSAR	QSAR prediction	No indication identified that model was operating outside of its operational limits
		No alert found	OASIS (in OECD QSAR)	QSAR prediction	No indication identified that model was operating outside of its operational limits
	Androgen receptor binding activity	-2.73 to -10000 log RBA	FDA EKDB model	Model drew comparison with dibutyl adipate, di(2-ethylhexyl) adipate and di-i-butyl adipate	Model reports that on basis of only limited similarity with compounds in database (0.57-0.59), no conclusion should be drawn
	Estrogen gene activation	-10000 log RBA	FDA EKDB model	Model drew comparison with dibutyl adipate, di(2-ethylhexyl) adipate and di-i-butyl adipate	Model reports that on basis of only limited similarity with compounds in database (0.57-0.59), no conclusion should be drawn
	Estrogen receptor binding activity	Non binder, non-cyclic structure	OECD QSAR	QSAR prediction	No indication identified that model was operating outside of its operational limits
		-10000 log RBA	FDA EKDB model	Model drew comparison with di(2-ethylhexyl) adipate, Cineole and bis(n-octyl) phthalate	Model reports that on basis of only limited similarity with compounds in database (0.36-0.58), no conclusion should be drawn
Aquatic Toxicity	Unspecified taxa	Immobilisation EC_{50} = 0.00644 mg/L	OECD QSAR	QSAR estimation of immobilisation endpoint by uTOX (Multicase)	Reported to be within QSAR domain, hence considered acceptable
	Unspecified taxa	Mortality EC_{50} = 0.00644 mg/L	OECD QSAR	QSAR estimation for EC50 by uTOX (Multicase)	Reported to be within QSAR domain, hence considered acceptable
	Bacteria	EC_{50} = 0.00644 mg/l (5 min)	OECD QSAR	QSAR Prediction for *Vibrio fischer*i, from uTOX (Multicase)	Reported to be within QSAR domain, hence considered acceptable
Sources: *OECD QSAR Data obtained using OECD QSAR Toolbox at Internet site:* *http://www.oecd.org/chemicalsafety/assessmentofchemicals/theoecdqsartoolbox.htm#Download_qsar_application_toolbox* *FDA EKDB data obtained using FDA EKDB Database at Internet site:* *http://www.fda.gov/ScienceResearch/BioinformaticsTools/EndocrineDisruptorKnowledgebase/default.htm*					

Mammalian hazard profile

Toxicokinetics: based on expert opinion, it is suggested in the ECHA Dissemination Portal that TBC is expected to be readily absorbed orally but, if inhaled, availability is assumed to be low because of its low vapour pressure. TBC is also expected to be poorly absorbed dermally. Based on its $LogP_{ow}$ and water solubility, there is considered low risk of accumulation and it is believed to undergo extensive metabolism by esterases and Cyp_{P450} enzymes, and to undergo β-oxidation or enter the citric acid cycle or, potentially, glucuronidation. In support of this view, in a study reported on the ECHA Dissemination Portal by Davis (1991) previously cited by the US EPA, it is reported that TBC undergoes rapid metabolism in both human serum and rat liver homogenates with a half-life ($t_{½}$) of 4 hours to produce, it is suggested, acetic acid, citric acid and butanol; the latter would be expected to undergo further oxidisation to butanoic acid and reassimilation by ß-oxidation. Any non-metabolised parent compound will be excreted via the urine or, to a lesser extent, the biliary route.

Acute toxicity: in a paper by Finkelstein & Gold (1959) a LD_{50} values of >30 mL/kg bw and > 50 mL/kg are quoted for the Wistar rat and the cat respectively, though little information is available on the study methodology. However, it is suggested that, were TBC to be classified under CLP based on the rodent acute toxicity data available publicly from other sources (see LD_{50} values in rodents, Table 4.67), there would be a basis for considering classification as a Category 3 acute toxin. Information from Safety Data Sheets suggests it may be harmful if swallowed or inhaled (Acros Organics, 2009) (USP, 2009). The range of air MEG values established by the US Army (Table 4.67) suggests that there may be a basis for concern with regard to occupational atmospheric exposure to the substance and that risk management measures would be necessary to control worker exposure via this route.

Irritancy and sensitisation: as noted in Table 4.38 of the Non-confidential document, the ECHA C&L Inventory identifies 93 aggregated notifications in which TBC is given the H318 (causes serious eye damage) precautionary statement. Safety Data Sheets available on the Internet suggest that TBC is indicated as 'may cause irritation of the eye, skin, digestive tract and respiratory tract' (Acros Organics, 2009) (USP, 2009). The two QSAR modelling outputs (from a Danish EPA database source) that were reported to fall within domain were 'negative', thus providing no further insight into the irritancy potential of the substance (indeed, on the ECHA Dissemination Portal only read-across information is included). No experimental data are available on the sensitisation potential of the substance, though no concerns with regard to sensitisation potential activity were identified by QSAR modelling using the OECD toolbox.

Repeat dose toxicity: the ECHA Dissemination Portal cites findings from Finkelstein & Gold (1959) arising from a 2 month study in cats given TBC at a nominal dosage of 5 mL/kg bw; the reported information is inconsistent with regard to whether treatment was via the diet or by oral gavage. Effects were reported as limited to diarrhoea and weight loss of approximately 30% in treated animals. This paper also reported a study in an unspecified rat strain in which TBC was given via the diet at nominal levels of 5 or 10 %; it appears that the treatment groups comprised either 4 or 8 individuals and the control group 2 individuals. Lower weight gain and diarrhoea were apparent in the group given 10% but no effects were reported at the lower dosage. The ECHA Dissemination Portal also reports read-across considerations from a 13-week rat dietary study on the structurally related substance ATBC in which the highest dosage (1000 mg/kg bw/d) tested was established as a NOAEL. No other information has been identified on the repeat dose toxicity of TBC.

Genotoxicity and carcinogenicity: no substance-specific information is presented on the ECHA Dissemination Portal, but the overall weight of evidence with regard to the mutagenic and

clastogenic potential of TBC based on QSAR modelling indicates only low concern, with only one positive and one equivocal prediction being generated. The remainder of predictions were negative. TBC has not been assessed for carcinogenicity by IARC. Furthermore, QSAR predictions of carcinogenic potential, together with the apparent lack of genetic toxicity suggested by QSAR modelling, indicate that there is little basis for concern.

Reproductive and developmental toxicity: no data on the potential reproductive toxicity of this substance have been identified. Weight-of-evidence arguments supporting a lack of developmental toxicity, based on read-across from ATBC, are presented on the ECHA Dissemination Portal. A QSAR prediction originating from the TERIS database was also negative with respect to the potential teratogenicity of TBC.

Other toxicities: QSAR modelling of the substance's ability to interact with proteins, with the oestrogen receptor gene or with oestrogen or androgen receptors did not indicate concern with regard to its endocrine disruptive potential, although the predictions from the FDA EKDB model should not be regarded as reliable.

Environmental fate and behaviour and ecotoxicology

As noted in Table 4.67, TBC is included in the German Federal Environmental Agency List of Substances which are Hazardous to Water, but is given only a low hazard classification of 1 (i.e. low hazard to waters). In contrast, the notification in the ECHA C&L Inventory indicates that it has been considered to be a Class 1 acute aquatic toxin, warranting the hazard statement H400. According to the information presented on the ECHA Dissemination Portal, TBC does not warrant classification with respect to the environment. It is, however, reported to show an environmental hydrolysis half-life of between 1.918 and 19.183 years depending on method of calculation but to have an overall OH rate constant (gas-phase reaction constant) of 16.04 E^{-12} cm^3/molecules-sec with a half-life of 0.67 days (8.00 hours). Although it is stated to be readily biodegradable (74% degradation in 28 d), it was found to have a calculated bioconcentration factor (BCF) of 94.7 L/kg wet-wt. It is also noted that, on the ECHA Dissemination Portal, the PBT assessment for this substance is indicated as confidential. A GLP- compliant study to EU Method C.2 and OECD 2.2 in *Daphnia magna* established an EC_{50} of 90.76 mg/L for 24 h and 66.89 mg/L for 48 hr based on mobility while another GLP–compliant study - conducted using EU Method C.3 (OECD 201) for growth inhibition in algae - established a 72 h EC_{50} of 100.4 mg/L based on growth rate and 23.86 mg/L based on biomass yield.

There are no other publicly available data at this time to inform on the basis for this classification but the concerns raised by some bodies are reflected by predictions from the OECD QSAR toolbox, which suggest quite low EC_{50} values for immobilisation and mortality in an unspecified taxa (which may relate to invertebrate species) and for acute bacterial mortality. However, it was also predicted that it would be rapidly metabolised which, together with its established K_{ow} (see Table 4.37 of the Non-confidential document), suggests that there should be little concern with regard to its potential bioaccumulation. Overall, therefore, in the absence of an authoritative assessment of its environmental risk, there remains some uncertainty.

4.9.3.2 Comparison of hazards

Table 4.69 compares TBC to DBP in terms of DNEL values. The DNEL values for TBC are taken from the ECHA Dissemination Portal.

Table 4.69: Human health risk comparison between TBC and DBP

Parameter	TBC		DBP	
Workers				
Acute / short-term exposure - systemic effects	Dermal DN(M)EL		Dermal DN(M)EL	
	Inhalation DN(M)EL		Inhalation DNEL	2.84 mg/m³
Acute / short-term exposure - local effects	Dermal DN(M)EL		Dermal DN(M)EL	
	Inhalation DN(M)EL		Inhalation DN(M)EL	
Long-term exposure - systemic effects	Dermal DNEL	20.8 mg/kg bw/d	Dermal DNEL	0.19 mg/kg bw/day
	Inhalation DNEL	73.5 mg/m^3	Inhalation DNEL	0.13 mg/m³
Long-term exposure - local effects	Dermal DN(M)EL		Dermal DN(M)EL	
	Inhalation DN(M)EL		Inhalation DN(M)EL	
General population				
Acute / short-term exposure - systemic effects	Dermal DN(M)EL		Dermal DN(M)EL	
	Inhalation DN(M)EL		Inhalation DN(M)EL	
Acute / short-term exposure - local effects	Dermal DN(M)EL		Dermal DN(M)EL	
	Inhalation DN(M)EL		Inhalation DN(M)EL	
Long-term exposure - systemic effects	Dermal DNEL	12.5 mg/kg bw /d	Dermal DNEL	2.2 mg/kg bw/day
	Inhalation DNEL	28.8 mg/m^3	Inhalation DNEL	0.62 mg/m³
	Oral DNEL	12.5 mg/kg bw/d	Oral DNEL	0.22 mg/kg bw/day
Long-term exposure - local effects	Dermal DN(M)EL		Dermal DN(M)EL	
	Inhalation DN(M)EL		Inhalation DN(M)EL	

Sources:
CSR
European Chemicals Agency: http://echa.europa.eu/
Note that for the general population, the CSR does not include toxicological thresholds, as consumer exposure is not considered relevant to the uses of the substance. The figures noted above in the grey part of the Table are from the registration of DBP, as shown on the ECHA Dissemination Portal

Table 4.70 compares the environmental hazard profile of TBC with that of DBP, in terms of their proposed PNECs. The values for DBP are more stringent than those for TBC with the exception of PNECs for STP.

Table 4.70: Environmental risk comparison between TBC and DBP

Parameter	TBC		DBP	
Aquatic organisms				
Freshwater	PNEC aqua (freshwater)	67 µg/L	PNEC aqua (freshwater)	10 µg/L
Marine water	PNEC aqua (marine water)	6.7 µg/L	PNEC aqua (marine water)	1 µg/L
Intermittent releases	PNEC aqua (intermittent releases)	0.67 mg/L	PNEC aqua (intermittent releases)	
STP	PNEC STP	10.3 mg/L	PNEC STP	0.22 mg/L
Sediment (freshwater)	PNEC sediment (freshwater)	1.17 mg/kg sediment dw	PNEC sediment (freshwater)	1.19 mg/kg sediment dw
Sediment (marine water)	PNEC sediment (marine water)	0.117 mg/kg sediment dw	PNEC sediment (marine water)	0.119 mg/kg sediment dw
Air				
Air		No hazard		No hazard
Terrestrial organisms				
Soil	PNEC soil	0.92 mg/kg soil dw	PNEC soil	0.05 mg/kg soil dw
Predators				
Secondary poisoning	PNEC oral	222.22 mg/kg food	PNEC oral	1.33 mg/kg food
Sources: *CSR* *European Chemicals Agency: http://echa.europa.eu/*				

Finally, Table 4.71 provides a comparison of concerns arising from DBP and TBC by human health and environmental endpoints.

Table 4.71: Hazard comparison of dibutyl phthalate and TBC

Hazard endpoint	TBC	DBP
Human health		
Acute toxicity	Slight (oral, inhalation)	
Irritancy	Uncertain (conflicting reports of effects on eye, skin, digestive and respiratory tracts)	
Repeat dose		Toxic
STOT		Liver, kidney, testes
Reproductive toxicity		1B (male fertility)
Developmental toxicity		1B (males)
Carcinogenicity		Data are insufficient to determine the carcinogenic potential. No evidence of carcinogenicity is available. The CSR assumes that the substance is not a carcinogen
Environment		
Aquatic	Very toxic (acute)	Very toxic
Note: grey cells indicate areas where no relevant information is available		

Overall, TBC has a relatively low acute mammalian toxicity. Available experimental studies, though considered of limited reliability, suggest little concern as regards to its repeat dose toxicity. There is, however, an absence of data on its reproductive or developmental effects, though available QSAR predictions do not identify any specific concerns with regard to its developmental or endocrine toxicity. There is, also uncertainty as to if it is, or is not, irritant; this reflects the differences in the submissions of classifications for eye effects advised by different notifiers. Hence, potentially there might be a risk of irritancy for workers if exposed. With regard to its environmental toxicity, there is a degree of uncertainty as to the extent of hazard posed since the most conservative assessments available suggest TBC may pose a comparable hazard to the aquatic environment.

4.9.4 Economic feasibility

DEZA does not manufacture TBC as it is unfamiliar with the technology and process parameters required for its production but, primarily, due to a lack of demand for the substance by the DUs. Although TBC is an ester, it is currently not included in DEZA's product portfolio.

Importantly, due to the unproven technical feasibility of the substance from the perspective of DUs, it is unclear whether any of them would actually use TBC as a substitute of DBP. Moreover, even if TBC would prove to be technically feasible for the applicant's customers, the volume of current sales of DBP to propellant manufacturers that could be substituted with TBC would likely only be very modest, due to (a) the presence of other established suppliers (see Table 4.72) and (b) the overall small tonnage of moderant/plasticiser that is required in the uses of concern. Notably, TBC is considered to be technically inferior to ATBC; therefore, if DEZA felt compelled to start the manufacture of a citrate, the choice might be made to select ATBC rather than TBC.

As explained earlier for ATBC, a certain minimum tonnage of ester has to be manufactured before the economics of production become viable; the volume of current sales of DBP to propellant manufacturers cannot justify the investment cost associated with the setting up of a new production line for TBC, especially since DEZA would face strong competition from existing established suppliers of the substance.

This alternative substance cannot be considered economically feasible for the applicant.

Additional confidential information is presented in: AoA Confidential Annex DBP Propellants DEZA.pdf, Section 4.1.3

4.9.5 Availability

4.9.5.1 Current and projected availability

Availability for the applicant

As discussed above, TBC is manufactured using technology that is unknown to DEZA and its compatibility with the current esterification plant is uncertain. The applicant cannot manufacture TBC at present.

Availability for the downstream users

From the perspective of the DUs, the market availability of TBC is given in Table 4.72.

Table 4.72: Market availability of TBC

Alternative	Data availability	Market availability from the perspective of the downstream users
TBC	Limited	Available on the market REACH registered in May 2013; one registrant shown in ECHA Dissemination Portal (100-1,000 t/y)

4.9.5.2 Actions required for improving availability

Availability for the applicant

For TBC to become available to the applicant the ability of the existing esterification plant to manufacture TBC at sufficient quantities and in the required quality needs to be investigated, if there a market incentive for doing so.

The Confidential Annex to this AoA explains the tasks that the applicant would have to undertake in researching, trialling and starting the production of TBC at their plant. The time that would be required for such production to be initiated at the industrial scale would extend beyond the Sunset Date for the Authorisation of DBP even if DEZA started the process of researching the production of TBC as soon as this AfA was submitted.

The conclusion is that without a breakthrough in the DUs' R&D efforts, the availability of the substance for the applicant would be unlikely to improve in the foreseeable future.

Additional confidential information is presented in: AoA Confidential Annex DBP Propellants DEZA.pdf, Section 4.1.4

Availability for the downstream users

TBC is generally available on the market for use by propellant manufacturers.

4.9.6 Conclusion on suitability and availability of TBC

4.9.6.1 Technical suitability

The substance is not available to the applicant and it is manufactured with technology that is not currently known to the applicant, therefore it may not be considered technically feasible.

From the perspective of the DUs, TBC is described as appropriate for consideration both as an alternative surface moderant and as a plasticiser. The assessment of its suitability varies widely and it is likely that TBC could be suitable for use under current production processes for certain calibres only. Moreover, for TBC to be used as a substitute plasticiser, propellant formulations might need more fundamental re-formulation. Between ATBC and TBC, the former appears to be technically superior.

4.9.6.2 Reduction of overall risk

The (limited and sometimes conflicting) information available for TBC suggests that it probably poses a lower hazard to human health than DBP, though acute exposure to TBC may cause eye damage. Both substances have classification for effects to aquatic life and the nature and degree of environmental hazard posed by TBC appears uncertain. There is also an absence of documented

data on its reproductive effects, while no concerns have been raised with regard to either developmental or endocrine toxicity.

As the risks from exposure to DBP from its use in the formulation and subsequent use of propellants are adequately controlled, the use of TBC would not result in discernible benefits to DUs' workers' health.

4.9.6.3 Economic feasibility

Given the uncertain uptake of TBC by DUs, the applicant's lack of knowledge over the production conditions and the need to ensure that a minimum sales tonnage must be achieved before the production of a new ester compound can be profitable, TBC cannot be considered economically feasible for the applicant. This is particularly true because DEZA would have to compete against established suppliers of the substance.

4.9.6.4 Availability

From the perspective of the applicant, the substance is not available as its manufacture is based on technology not available to him. Moreover, the future availability of the substance is unlikely to change; the quantity of TBC that would be sold by DEZA is too small to justify the expense of setting up and operating a new production line based on new technology.

Key point 17

TBC could theoretically be considered both as an alternative moderant and an alternative plasticiser. In addition, it being an ester would allow DEZA to use its existing esterification plant for its production. However, the technical feasibility of ATBC for DEZA is limited and the economics of production are unfavourable. TBC appears to pose lower a lower human health hazard but warrants concern with regard to its toxicity to the aquatic environment

i) ALTERNATIVE SUBSTANCE: DIOCTYL AZELATE

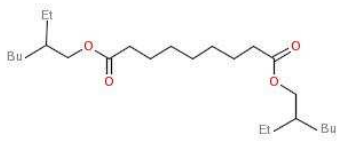
4.10 Dioctyl azelate

4.10.1 Substance ID and properties

4.10.1.1 Name and other identifiers for the substance

The following Table presents the identity of DOZ.

Table 4.73: Identity of DOZ

Parameter	Value	Source
EC number	203-091-7	1
EC name	Bis(2-ethylhexyl) azelate	
CAS number	103-24-2	1
IUPAC name	Bis(2-ethylhexyl) azelate	2
Other names	Dioctyl azelate Bis(2-ethylhexyl) nonanedioate Nonanedioic acid, bis(2-ethylhexyl) ester Azelaic acid, bis(2-ethylhexyl) ester Emolein 2986	2
Molecular formula	$C_{25}H_{48}O_4$	1
SMILES notation	O=C(OCC(CC)CCCC)CCCCCCCC(=O)OCC(CCCC)CC	2
Molecular weight	412.65	2
Molecular structure		1

Sources:
1 : ESIS Internet site : http://esis.jrc.ec.europa.eu/
2 : Chemspider Internet site : http://www.chemspider.com/Chemical-Structure.7359.html

4.10.1.2 Composition of the substance

No information is available on constituents and impurities. The substance is registered as being available at between 100 and 1000 t/y on ECHA's Dissemination Portal[39].

[39] Date of last search: 26 June 2013.

4.10.1.3 Physico-chemical properties

The following Table summarises the available information on the physico-chemical properties of DOZ. The information has been collected from a variety of literature sources and through consultation with stakeholders.

Table 4.74: Physico-chemical properties of DOZ

Property	Value	Remarks	Source
Physical state at 20°C and 101.3 kPa	Clear liquid		3
Melting/freezing point	40.52°C	MPBPWIN v1.42: Mean or Weighted MP	1
	-78°C	From literature	2, 4
	-65°C	Consultation response	
Boiling point	416.97°C at 101.3 kPa	ACD/PhysChem Suite	1
	414.02°C	MPBPWIN v1.42: Adapted Stein & Brown method	1
	376°C		3
	237 °C at 0.67 kPa	From literature	4
Density	0.919 g/cm^3	ACD/PhysChem Suite	1
	0.915 g/cm^3 at 25°C		2, 6
Vapour pressure	0 kPa at 25°C	ACD/PhysChem Suite	1
	5 x 10^{-7} kPa at 25°C	Modified Grain method	1
	<3.12 x 10^{-7} kPa at 80°C	Measured	5
	1.82 x10^{-10} kPa at 20°C		6
Surface tension	32.395 dyne/cm	ACD/PhysChem Suite	1
Water solubility	1.655 x 10^{-5} mg/L at 25°C	WSKOW v1.41, LogK$_{ow}$ used: 9.59 (estimated)	1
	3.51 x 10^{-5} mg/L	Wat Sol (v1.01 est): Estimate from Fragments	1
	Insoluble		2
	<0.0004 mg/L at 20 °C	Measured	5
Partition coefficient n-octanol/water	9.59	KowWin	1, 6
	11.9 at 25°C	Measured	5
Flash point	184.61°C	ACD/PhysChem Suite	1
	221°C		3
	240°C	ISO FF102400	6
Flammability	No data		
Explosive properties	No data		
Self-ignition temperature	No data		
Oxidising properties	No data		
Granulometry	Not relevant		

Sources:
1: ChemSpider Internet site : http://www.chemspider.com/Chemical-Structure.7359.html
2: Lide, D.R. (ed.). CRC Handbook of Chemistry and Physics. 79th ed. Boca Raton, FL: CRC Press Inc., 1998-1999., p. 3-224 (referenced at http://toxnet.nlm.nih.gov/cgi-bin/sis/search/r?dbs+hsdb:@term+@rn+@rel+103-24-2)
3: Parchem Internet site: http://www.parchem.com/chemical-supplier-distributor/Dioctyl-Azelate-001612.aspx
4: US EPA Internet site: http://ofmpub.epa.gov/oppthpv/Public_Search.PublicTabs?section=1&SubmissionID=24945803&epcount=8&epname=null&epdiscp=null&selchemid=101121&CategorySingle=Category
5: OECD Internet site: http://webnet.oecd.org/Hpv/UI/handler.axd?id=0f640506-2220-4aae-b3b3-de685d164cff
6: European Chemicals Agency: http://echa.europa.eu/

4.10.1.4 Classification and labelling

According to ECHA's C&L Inventory, a total of 63 notifiers[40] have not notified any classification for the substance.

4.10.1.5 REACH Registration details

The following Table summarises the available information on the status of REACH Registration for DOZ.

Table 4.75: REACH Registration status of DOZ

Registration	Result	Date of last search
Pre-registered	Yes	4 June 2012
Registered	Yes – 100-1,000 t/y	26 June 2013
Source: *European Chemicals Agency: http://echa.europa.eu/*		

4.10.2 Technical feasibility

4.10.2.1 Technical feasibility from the perspective of the applicant

DEZA does not currently manufacture this substance and does not have any current plans to start production in the future without a clear indication from its DUs that DOZ would be a technically feasible and acceptable alternative.

DEZA has experience in esterification reactions and the manufacture of DOZ would involve an esterification reaction with raw materials different to those of DBP. The Confidential Annex to this AoA explains that DEZA's ability to obtain the precursors to DOZ, which the company does not currently manufacture.

Overall, the applicant cannot manufacture DOZ at present; the manufacture of azelates at DEZA's esterification plant is only a theoretical possibility. Technically, this alternative cannot be considered feasible for the applicant at present.

Additional confidential information is presented in: AoA Confidential Annex DBP Propellants DEZA.pdf, Section 4.1.2

4.10.2.2 Technical feasibility from the perspective of downstream users

Relevance as substitute for DBP

According to consultation, the relevance of the substance as a substitute for DBP in propellant mixtures is as follows:

Substance family	Azelates (esters of nonanedioic acid)
Function	Plasticiser

[40] Date of search: 26 June 2013.

With particular regard to the potential use of the substance as a moderant, it is unsuitable for use due to its particularly long molecular chain, which impedes its diffusion to the surface of the propellant grain. Therefore, DOZ would only be technically feasible for use in a very small proportion of propellant powders that currently rely on DBP.

Background to the use of the substance

Functions of DOZ in propellants: no information has been found in the open literature that would confirm the current use of DOZ in solid gun propellants for the applications of concern. The presence of the substance has been suggested, mainly within patents, for:

- composite propellants based on hydroxyl-terminated polybutadiene (HTPB) binder rather than nitrocellulose (Chassaing & Finck, 1998) (Libardi, Ravagnani, Morais, & Cardoso, 2010);
- composite propellants based on polyurethane binders (Aerojet-General Corporation, 1974) (Nichols, 1974); and
- propellants used in rockets (Agrawal, 2010).

Non-explosive uses of DOZ: according to the information provided by a Japanese manufacturer during the preparation of a SIDS (Screening Information Dataset) Document for the substance, the main use (up to 95%) of DOZ was as a plasticiser for cellulosics, polystyrene and vinyl plastics in order to improve their resistance and to avoid the development of cracks under low temperature conditions. A limited amount of the substance was also used as a lubricant at industrial sites (OECD, 2006). Other materials that may be plasticised with DOZ include (Wypych, 2004):

- ethylene vinyl acetate (EVA) polymer (e.g. biodegradable shrink films); and
- polylactides (e.g. biodegradable shrink films).

Notably, DOZ is used in applications which require low temperature properties similar to those obtained by DEHA but with better retention of the plasticiser because of its lower volatility.

Comparison against key technical feasibility and selection criteria

Trials with the substance and perceived overall technical suitability: this information is presented in the Confidential Annex.

Comparison against the key technical feasibility and selection criteria: this information is presented in the Confidential Annex.

Additional confidential information is presented in: AoA Confidential Annex DBP Propellants DEZA.pdf, Section 4.10.2.2

4.10.3 Reduction of overall risk due to transition to the alternative

4.10.3.1 Hazard and risk information

In addition to the information on the ECHA Dissemination Portal, information on the hazards and risks from DOZ is available from a 2006 SIDS Initial Assessment Report that was prepared by the Japanese authorities and is available on the OECD Internet site, as well as from other publicly available sources. To supplement the information available from these sources, QSAR models (OECD QSAR toolbox and FDA EKDB models) were employed to fill data gaps and help in

understanding the mammalian hazard and ecotoxicological profile of the substance. Relevant outputs of the QSAR modelling (and associated references) are presented in Table 4.76, overleaf.

Based on all available information, the hazard profile of this substance may be summarised as follows.

Mammalian hazard profile

Toxicokinetics: no information on toxicokinetics was presented on the ECHA Dissemination Portal or in the OECD SIDS Document and no robust QSAR predictions were generated. However, based on the physico-chemical properties of DOZ (Table 4.41 of the Non-confidential document), dermal intake would be anticipated to be low.

Acute toxicity: in a rat acute oral toxicity study conducted according to OECD TG401 under GLP that was described in the OECD assessment, male and female Crj:CD (SD) IGS rats (five animals/sex/dose) were given DOZ by gavage at up to 2,000 mg/kg bw without significant adverse effects. The oral LD_{50} value was therefore established as greater than 2,000 mg/kg bw (OECD, 2006). The ECHA Dissemination Portal also reports this study as Shirota (2003). In addition, in an acute dermal study in the albino rabbit by Smyth *et al* (1962) cited on the ECHA Dissemination Portal, a dermal LD_{50} of 20 mL/kg bw (18,200 mg/kg bw) is reported.

Irritation and sensitisation: skin irritation of rabbits was assessed using a 10-grade ordinal series (based upon the most severe reaction that developed on the clipped skin of each of five rabbits within 24 hours of uncovered application of 0.01 mL); grade 1 indicated no irritation and grade 10 indicated necrosis from a 0.01% solution. Dermal irritation from DOZ was grade 3 (OECD, 2006). Similarly, ocular irritancy/corrosivity was assessed using a grading system where Grade 1 indicated at most a very small area of necrosis resulting from 0.5 mL of undiluted chemical in the eye, and grade 10 indicated a severe burn from 0.5 mL of a 1% solution. For DOZ, irritation was Grade 1 only (OECD, 2006). This suggests that DOZ is only weakly irritant to skin and very weakly irritant to the eye. No additional primary irritancy studies are cited on the ECHA Dissemination Portal.

Although no information on sensitisation is presented in the OECD SIDS Document, the ECHA Dissemination Portal cites an unpublished Murine Local Lymph Node Assay conducted to GLP, which identified an apparently elevated response (particularly when using undiluted test material) in treated compared with control animals; this finding was considered ambiguous by the Registrant and no classification was proposed. A QSAR prediction from the Danish EPA Database was negative (see Table 4.76).

Repeated dose toxicity: in an OECD compliant (TG 422) reproductive and developmental screening study conducted to GLP, Crj:CD (SD) IGS rats (13 animals/sex/dose) were orally dosed by gavage at dosages of up to 1,000 mg/kg bw/day; this study is also reported as Shirota (2003) on the ECHA Dissemination Portal. In this, males were dosed by oral gavage for 42 days beginning 14 days before mating, while females were dosed for 42-53 days from 14 days before mating to Day 4 of lactation. General clinical observations and detailed clinical pathology and neurobehaviour testing was undertaken for both sexes. A repeat dose LOAEL of 1,000 mg/kg bw/day and a NOAEL of 300 mg/kg bw/day were established, based on effects on body weight gain, hepatic pathological and haematological, and biochemical changes (OECD, 2006).

Table 4.76: Human health and environmental hazard profile for DOZ

Hazard endpoint		Finding	Data source	Study design	Assessed robustness/Comment
Sensitisation	In vivo - Skin sensitisation	Negative	OECD QSAR	QSAR prediction by skin sensitisation, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
Genetic toxicity	In vitro - Mutagenicity	Negative	OECD QSAR	QSAR prediction by DNA reactivity (based on Ashby fragments), from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
	In vivo - Mutagenicity	Negative	OECD QSAR	QSAR prediction by Drosophila sex-linked recessive lethal test, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
	In vivo – Chromosomal effect	Negative	OECD QSAR	QSAR prediction by mouse micronucleus assay, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Negative	OECD QSAR	QSAR estimation for Rodent, Dominant lethal assay (chromosome aberration) from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
Carcinogenicity		Positive	OECD QSAR	QSAR prediction based on FDA Cancer Male Mouse, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Negative	OECD QSAR	QSAR prediction based on Mouse lymphoma, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		TD_{50} = 1000 mg/kg/day	OECD QSAR	QSAR prediction by mouse Carcinogenic Potency Database (CPDB), from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Negative	OECD QSAR	QSAR prediction based on FDA Cancer Female Rat, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Negative	OECD QSAR	QSAR prediction based on FDA Cancer Male Rat, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		TD_{50} = 1000 mg/kg/day	OECD QSAR	QSAR prediction by rat Carcinogenic Potency Database (CPDB), from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
Developmental toxicity / Teratogenicity		Negative	OECD QSAR	QSAR prediction based on FDA Teratogen Information System (TERIS), from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
Other toxic endpoints	Protein binding potential	No alert found	OECD QSAR	QSAR prediction	No indication identified that model was operating outside of its operational limits
		No alert found	OASIS (in OECD QSAR)	QSAR prediction	No indication identified that model was operating outside of its operational limits

Hazard endpoint		Finding	Data source	Study design	Assessed robustness/Comment
	Androgen receptor binding activity	-2.73 to -10000 log RBA	FDA EKDB model	Model drew comparison with Di(2-Ethylhexyl) adipate, Dibutyl adipate and Di-i-butyl adipate	Model reports that on basis of similarity results (0.94-1), DOZ may be active
	Estrogen gene activation	-10000 log RP	FDA EKDB model	Model drew comparison with Di(2-Ethylhexyl) adipate, Dibutyl adipate and Di-i-butyl adipate	Model reports that on basis of similarity results (0.94-1), DOZ does not seem to be active
	Estrogen receptor binding activity	Negative	OECD QSAR	QSAR prediction by relative estrogen receptor binding activity, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		10%	OECD QSAR	QSAR prediction by estrogen receptor binding activity (Multicase)	Reported to be outside of QSAR domain, hence considered of doubtful reliability
		Non binder, non-cyclic structure	OECD QSAR	QSAR prediction	No indication identified that model was operating outside of its operational limits
		-10000 log RBA	FDA EKDB model	Model drew comparison with di(2-Ethylhexyl) adipate, cineole and suberic acid	Model reports that on basis of similarity results (0.64-1), DOZ does not seem to be active

Sources:
OECD QSAR Data obtained using OECD QSAR Toolbox at Internet site:
http://www.oecd.org/chemicalsafety/assessmentofchemicals/theoecdqsartoolbox.htm#Download_qsar_application_toolbox
FDA EKDB data obtained using FDA EKDB Database at Internet site:
http://www.fda.gov/ScienceResearch/BioinformaticsTools/EndocrineDisruptorKnowledgebase/default.htm

Genotoxicity and carcinogenicity: in several reverse gene mutation assays (on *S typhimurium* TA98, TA100, TA1535, TA1537 and *E. coli* WP2uvrA, both with and without metabolic activation) conducted to OECD TG 471 and the Japanese Guideline for Screening Mutagenicity Testing of Chemicals (Chemical Substances Control Law of Japan), and in compliance with GLP, growth inhibition was not observed at up to 5,000 µg/plate for any species or strain and, therefore, DOZ was not considered to be mutagenic (OECD, 2006). In a chromosomal aberration test (OECD TG 473) in cultured Chinese hamster lung (CHL/IU) cells conducted to GLP, using concentrations of 150 - 2,400 µg/mL (for a 6 hour short treatment, with and without metabolic activation) and at 38-600 µg/mL (for 24 hour continuous treatment, without metabolic activation), no effects on polyploidy or incidence of chromosomal aberrations were observed in the absence of evidence of cell toxicity (OECD, 2006). These experimental findings are also further supported by negative findings from QSAR modelling of in vivo mutagenic and chromosomal effects (see Table 4.76).

Although no information on carcinogenicity was presented in the OECD SIDS Document, in most cases, QSAR modelling of carcinogenic potential (Table 4.76) raised few concerns, indicating low potential for carcinogenicity although a positive prediction was generated by the FDA Cancer Male Mouse model.

Reproductive and developmental toxicity: the robust screening study mentioned above in respect of repeat dose toxicity, also provides insight into the reproduction and developmental toxicity of DOZ when given by oral gavage at up to 1,000 mg/kg bw/day for either 42 or 42-55 days, to males or females respectively. No adverse reproductive effects were reported even at 1,000 mg/kg bw/day (which was identified as the repeat dose toxic LOAEL). Hence, the NOAEL for reproductive toxicity is 1,000 mg/kg bw/day. Furthermore, no significant changes in the number of implantations or in total numbers of pups or live pups were reported. The indexes for implantation, delivery, birth and live birth were also unaffected and there were no treatment-related changes in body weight, external appearance or pathology in the F1 (offspring) generation. Hence, the NOAEL for developmental toxicity was also considered to be 1,000 mg/kg bw/day (OECD, 2006). The absence of any developmental toxicity of DOZ is further supported by the negative prediction from QSAR modelling, based on the FDA Teratogen Information System (TERIS).

Other toxicities: endocrine receptor interactions are not addressed in either the SIDS dossier or the ECHA Dissemination Portal. However, QSAR modelling of the substance's ability to interact the androgen receptor suggested a possible cause for concern. No similar activity was predicted in the QSAR modelling of interaction with proteins, the oestrogen receptor or oestrogen receptor gene. Given the absence of any collaborative indications of significant reproductive or developmental toxicity in a robust experimental study, the significance of the prediction for the androgen receptor is considered doubtful.

<u>Environmental fate and behaviour and ecotoxicology</u>

The photochemical half-life of DOZ in air has been calculated as 0.4 day (rate constant: 2.959×10^{-11} cm^3/molecule-sec, OH radical concentration: 1.5×10^6 molecule/cm^3, and irradiation time: 12 hours/day) (OECD, 2006). If released to air, an estimated vapour pressure of 5.04×10^{-7} kPa at 25°C indicates DOZ will exist in both the vapour and particulate phases. The vapour-phase DOZ would be anticipated to degrade by photochemical reaction, with an estimated half-life of 13 hours; on the ECHA Dissemination Portal, an estimate of 13.013 hr is also given based on the US EPA AOPWIN v.1.92 model. However, particulate-phase DOZ would be expected to be removed by wet and dry deposition. If released from air into water, DOZ is expected to rapidly adsorb onto suspended solids and sediment in water (given its estimated K_{oc} of 300,000). Volatilisation from water surfaces is expected to be an important process based upon this compound's estimated Henry's Law constant (HSDB, undated). Additionally, hydrolysis in water is not expected to be

important given its very low water solubility (<0.0004 mg/L at 20°C), with a calculated half-life in water (pH 7) of 3.2 years (based on HYDROWIN modelling) (OECD, 2006).

Distribution modelling using Mackay Level III modelling indicates that sediment (67.5%) and soil (28.6%) are the main target compartments at 25°C and that volatilisation from the water phase is unlikely. The estimated soil sorption coefficient of log K_{ot} at 5.484 indicates that the substance will strongly absorb onto soil (OECD, 2006). Volatilisation from moist soil surfaces would be expected to be an important process governing its fate in the environment, based upon an estimated Henry's Law constant of 1.2 x 10^{-4} atm-m^3/mol. However, this process is expected to be attenuated by adsorption (HSDB, undated).

A ready biodegradability study (OECD TG301 C) showed DOZ to be readily biodegradable (>94% by BOD, 28 days), with both DOC (dissolved oxygen concentration) and GC analysis showing complete biodegradation and an absence of transformed products. More than 60% of biodegradation (BOD) occurs within 7-8 days, and the 10-day criteria were fulfilled. No information on inherent or anaerobic biodegradability was available (OECD, 2006). Another OECD 301B test reported by the US EPA High Production Volume Information System indicated a biodegradation of 81% in 28 days (average of duplicates)[41]. A bioconcentration factor of 3.2 can be derived from a calculated log P_{ow} value, using BCFWIN v2.15 (OECD, 2006). This value indicates that the potential for bioconcentration in aquatic organisms is low (HSDB, undated). Experimental data derived from Test Guideline and GLP compliant studies are also available to inform on the substance's acute and chronic toxicity in various taxal groups. This information may be summarised as follows.

Acute toxicity: from Table 4.77, it is apparent that preliminary tests show that DOZ exhibits no adverse effects at the limit of water solubility. Limit tests in fish, daphnids and algae at nominal concentrations of 0.1 mg/L (a dispersant of HCO-40 was used at the final concentration of 1.0 mg/L in each test) were conducted, with the resultant estimates of LC_{50} or EC_{50} values ranging from >0.08 mg/L to >10,000 mg/L depending on species. Analytical monitoring of test concentrations indicated a fall in concentration during the course of each test. As hydrolysis is unlikely, adsorption to glassware was suspected as the main reason (OECD, 2006).

[41] Available at: http://ofmpub.epa.gov/oppthpv/Public_Search.PublicTabs?section=1&SubmissionID=24945803&epcount=8&epname=null&epdiscp=null&selchemid=101121&CategorySingle=Category.

Table 4.77: Experimental studies on the acute aquatic toxicity of DOZ

Species	Method	Exposure	Result
Oryzias latipes	OECD TG 203 Limit test GLP	96 h semi-static	LC_{50} > 0.072 mg/L > W.S, (measured, mean)
Daphnia magna	OECD TG 202 Limit test GLP	48 h semi-static	EC_{50} > 0.093 mg/L> W.S. (measured, mean)
Pseudokirchneriella subcapitata	OECD TG 201 Limit test GLP	72 h static, open system	(Rate method) ErC_{50} >0.08 mg/L> W.S. (Biomass method) EbC_{50} >0.08 mg/L> W.S. (nominal)
Cyprinus carpio	OECD 203	96 h static	LD_{50} >10,000 mg/L
Sources: (OECD, 2006) *US EPA HPVIS Internet site:* *http://ofmpub.epa.gov/oppthpv/Public_Search.PublicTabs?section=1&SubmissionID=24964039&epcount=13&epname=null&epdiscp=null&selchemid=101121&CategorySingle=Category* *W.S.; Water Solubility (<0.0004 mg/L)* *Further unpublished studies are further quoted on the ECHA Dissemination Portal: European Chemicals Agency: http://echa.europa.eu/*			

Chronic toxicity: reliable test results available for chronic toxicity are summarised in Table 4.78.

Table 4.78: Experimental studies on the chronic aquatic toxicity tests of DOZ

Species	Method	Exposure	Result
Daphnia magna	OECD TG 211 Limit test GLP	21 d semi-static	(Reproduction) 21 d EC_{50} >0.064 mg/L> W.S. 21 d NOEC ≥0.064 mg/L> W.S. (measured, time-weighted mean)
Pseudokirchneriella subcapitata	OECD TG 201 GLP	72 h static, open system	(growth rate method) NOEC ≥0.08 mg/L>W.S. (biomass method) NOEC ≥0.08 mg/L>.W.S.
Source: (OECD, 2006) *W.S.; Water Solubility (< 0.0004 mg/L)*			

The available acute and chronic aquatic toxicity data for this substance suggest that there are no adverse effects for the aquatic compartment up to the limit of solubility and, overall, DOZ is judged as not PBT or vPvB (ECHA Dissemination Portal).

4.10.3.2 Comparison of hazards

The ECHA Dissemination Portal provides no DN(M)EL or PNEC values for DOZ and only indicates the lack of hazard for all endpoints and compartments. The following Table compares the information available on the hazards of DOZ with those of DBP.

Table 4.79: Hazard comparison of DBP and DOZ

Hazard endpoint	DOZ	DBP
Human health		
Acute toxicity	Very low (oral)	
Irritancy	Weak (skin, eye)	
Repeat dose		Toxic
STOT		Liver, kidney, testes
Reproductive toxicity		1B (male fertility)
Developmental toxicity		1B (males)
Carcinogenicity		Data are insufficient to determine the carcinogenic potential. No evidence of carcinogenicity is available. The CSR assumes that the substance is not a carcinogen
Environment		
Aquatic		Very toxic
Other		
Other issues	Possible endocrine activity (QSAR prediction of androgen receptor interaction potential)	
Note: grey cells indicate areas where no relevant information is available		

Experimental data, together with supplementary QSAR model predictions where considered appropriate, have identified no significant concerns with regard to either DOZ's human health or environmental toxic potential and, other than the questionable significance of the QSAR prediction of androgen receptor interaction potential and the ambiguous findings in a Murine Local Lymph Node Assay, it is apparent that the substance has a more benign hazard profile than DBP.

4.10.4 Economic feasibility

DEZA does not manufacture DOZ as it is unfamiliar with the technology and process parameters required for its production but, primarily, due to a lack of demand for the substance by the DUs. Although DOZ is an ester, it is currently not included in DEZA's product portfolio.

Importantly, due to the unproven technical feasibility of the substance from the perspective of DUs, it is unclear whether any of them would actually use DOZ as a substitute of DBP. Moreover, even if DOZ would prove to be technically feasible for some of the applicant's customers, the volume of current sales of DBP to propellant manufacturers that could be substituted with DOZ would likely only be very modest, due to (a) the fact that DOZ could only be used as a substitute plasticiser, thus would be potentially suitable to replace <<10% of the tonnage of DBP currently used by the applicant's DUs, and (b) the presence of other established suppliers (see Table 4.80).

As explained for other alternative substances, a certain minimum tonnage of ester has to be manufactured before the economics of production become viable; the volume of current sales of DBP to propellant manufacturers cannot justify the investment cost associated with the setting up of a new production line for DOZ, especially since DEZA would face strong competition from established suppliers of the substance.

This alternative substance cannot be considered economically feasible for the applicant. Under a refused Authorisation, sales of DBP to propellant manufacturers would be lost and could only be replaced by a much more modest level of DOZ sales, if any at all.

Additional confidential information is presented in: AoA Confidential Annex DBP Propellants DEZA.pdf, Section 4.1.3

4.10.5 Availability

4.10.5.1 Current and projected availability

Availability for the applicant

As discussed above, DOZ is manufactured using technology that is unknown to DEZA and its compatibility with the current esterification plant is uncertain as is uncertain the accessibility to the acid precursor to DOZ. The applicant cannot manufacture DOZ at present.

Availability for the downstream users

From the perspective of the DUs, the market availability of DOZ is given in Table 4.80.

Table 4.80: Market availability of DOZ

Alternative	Data availability	Market availability from the perspective of the downstream users
DOZ	Very limited	Uncertain availability REACH registered in May 2013; one registrant shown in ECHA Dissemination Portal

4.10.5.2 Actions required for improving availability

Availability for the applicant

For DOZ to become available to the applicant the ability of the existing esterification plant to manufacture DOZ at sufficient quantities, if there a market incentive for doing so.

The Confidential Annex to this AoA explains the tasks that the applicant would have to undertake in researching, trialling and starting the production of DOZ at their plant. The time that would be required for such production to be initiated at the industrial scale would extend beyond the Sunset Date for the Authorisation of DBP even if DEZA started the process of researching the production of DOZ as soon as this AfA was submitted.

The conclusion is that the availability of the substance for the applicant would be unlikely to improve in the foreseeable future.

Additional confidential information is presented in: AoA Confidential Annex DBP Propellants DEZA.pdf, Section 4.1.4

Availability for the downstream users

DOZ is potentially available on the market for use by propellant manufacturers.

4.10.6 Conclusion on suitability and availability of DOZ

4.10.6.1 Technical suitability

The substance is not available to the applicant and it is manufactured with technology that is not currently known to him, therefore it may not be considered technically feasible.

From the perspective of DUs, DOZ might potentially be suitable as a plasticiser but not as a surface moderant. As such, it cannot be a suitable substitute for the vast majority of the propellant mixtures that currently contain DBP. Given the virtually non-existent experience of the propellant manufacturers with the substance, a meaningful comparison of technical suitability to that of DBP cannot be provided.

4.10.6.2 Reduction of overall risk

The available information indicates that DOZ generally poses a low hazard to human health and the environment. However, as the risks from exposure to DBP from its use in the formulation and subsequent use of propellants are adequately controlled, the use of DOZ would not result in discernible benefits to DUs' workers' health.

4.10.6.3 Economic feasibility

Given the uncertain uptake of DOZ by DUs, the applicant's lack of knowledge over the production conditions and the need to ensure that a minimum sales tonnage must be achieved before the production of a new ester compound can be profitable, DOZ cannot be considered economically feasible for the applicant. This is particularly true because the amount of DBP currently used as a plasticiser in propellants is considerably low.

4.10.6.4 Availability

From the perspective of the applicant, the substance is not available. Moreover, the future availability of the substance is unlikely to change; the quantity of DOZ that could theoretically be sold by DEZA in the future would be too small to justify the expense of setting up and operating a new line.

Key point 18

DOZ appears to perform poorly against DBP and may only be considered as a potential substitute plasticiser. The experience of propellant manufacturers with the substance is practically non-existent. The substance poses lower hazards to human health and the environment but risks from DBP are already adequately controlled. Its economic feasibility and availability are unacceptable to the applicant

j) ALTERNATIVE SUBSTANCE: ISODECYL PELARGONATE

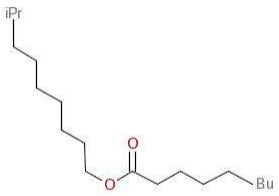
4.11 Isodecyl pelargonate

4.11.1 Substance ID and properties

4.11.1.1 Name and other identifiers for the substance

The following Table presents the identity of IDP.

Table 4.81: Identity of IDP

Parameter	Value	Source
EC number	203-665-7	1
EC name	8-methylnonyl nonan-1-oate	1
CAS number	109-32-0	1
IUPAC name	8-Methylnonyl nonanoate	
Other names	Isodecyl pelargonate Nonanoic acid, 8-methylnonyl ester	2
Molecular formula	$C_{19}H_{38}O_2$	1
SMILES notation	O=C(OCCCCCCCCC(C)C)CCCCCCCC	2
Molecular weight	298.5	2
Molecular structure		1
Sources: *1: ESIS Internet site: http://esis.jrc.ec.europa.eu/* *2: Chemspider Internet site: http://www.chemspider.com/Chemical-Structure.60316.html*		

4.11.1.2 Composition of the substance

No information is available on constituents and impurities. The substance does not appear on ECHA's database of registered substances[42].

4.11.1.3 Physico-chemical properties

The following Table summarises the available information on the physico-chemical properties of IDP. The information has been collected from a variety of literature sources and through consultation with stakeholders.

[42] Date of last search: 5 July 2013.

Table 4.82: Physico-chemical properties of IDP

Property	Value	Remarks	Source
Physical state at 20°C and 101.3 kPa	Clear liquid		3
Melting/freezing point	-73°C		3
	-80°C	Consultation response	
Boiling point	340.718°C at 101.3 kPa		1
	341.90°C	MPBPWIN v1.42: Adapted Stein & Brown method	1
	150°C	Consultation response	
Density	0.863 g/cm^3		1
Vapour pressure	0 mmHg at 25°C		1
	0.99 x 10^{-5} at 25°C	MPBPWIN v1.42: Modified Grain method	1
Surface tension	30.05 dyne/cm		1
Water solubility	0.001354 mg/L at 25°C	WSKOW v1.41 (log Kow used: 8.16 (estimated))	1
	0.0019468 mg/L	Wat Sol (v1.01 est), from Fragments	1
	< 2 mg/L	(Kaplan & Kaplan, 1985)	
Partition coefficient n-octanol/water	8.16	KowWin est	1
Flash point	162.152°C		1
	172°C		2
Flammability	No data		
Explosive properties	No data		
Self-ignition temperature	No data		
Oxidising properties	No data		
Granulometry	Not relevant		

Source:
1: Chemspider Internet site: http://www.chemspider.com/Chemical-Structure.60316.html
2: Island Pyrochemical Industries Internet site: http://www.islandgroup.com/specs/isodecyl_pelargonate.php
3: Rocket Motor Components Internet site: http://www.rocketmotorparts.com/pdfs/idp_msds_cognis.pdf

4.11.1.4 Classification and labelling

A search on the ECHA C&L Inventory[43] using the CAS number for the substance has identified only a single notifier that has not classified the substance.

[43] Date of last search: 5 July 2013.

4.11.1.5 REACH Registration details

The following Table summarises the available information on the status of REACH Registration for IDP.

Table 4.83: REACH Registration status of IDP

Registration	Result	Date of last search
Pre-registered	Yes – Envisaged Registration deadline: 30/11/2010	4 June 2012
Registered	No	5 July 2013
Source: *European Chemicals Agency: http://echa.europa.eu/*		

4.11.2 Technical feasibility

4.11.2.1 Technical feasibility from the perspective of the applicant

DEZA does not currently manufacture this substance and does not have any current plans to start production in the future without a clear indication from its DUs that IDP would be a technically feasible and acceptable alternative.

DEZA has experience in esterification reactions and the manufacture of IDP would involve an esterification reaction with raw materials different to those of DBP. The Confidential Annex to this AoA explains that DEZA's ability to obtain the precursors to IDP, which the company does not currently manufacture.

Overall, the applicant cannot manufacture IDP at present; the manufacture of pelargonates at DEZA's esterification plant is only a theoretical possibility. Technically, this alternative cannot be considered feasible for the applicant at present.

Additional confidential information is presented in: AoA Confidential Annex DBP Propellants DEZA.pdf, Section 4.1.2

4.11.2.2 Technical feasibility from the perspective of downstream users

Relevance as substitute for DBP

According to consultation, the relevance of the substance as a substitute for DBP in propellant mixtures is as follows:

Substance family	Nonanoic acid esters (pelargonates)
Function	Plasticiser

With particular regard to the potential use of the substance as a surface moderant, it is unsuitable for such a role due to its particularly long molecular chain, which impedes its diffusion to the surface of the propellant grain.

Background to the use of the substance

Functions of IDP in propellants: information on the use of IDP in propellants is abundant in the open literature, primarily in the form of patents. However, the substance does not appear to be used

in the types of nitrocellulose-based propellants that are of concern. More specifically, IDP has been reported as suitable for use in:

- solid rocket propellants (Jones & Tzeng, 2011);
- gun propellants based on triaminoguanidine ethylenedinitramine and cyclotetramethylene tetranitramine (Flanagan & Haury, 1976);
- triaminoguanidine nitrate LOVA (low vulnerability ammunition) propellants (Kaplan & Kaplan, 1985); and
- polybutadiene-acrylic acid-acrylonitrile (PBAN) terpolymer and hydroxyl terminated polybutadiene (HTPB)-based composite propellants (Muthiah, Somasundaran, Verghese, & Thomas, 1989).

Non-explosive uses of IDP: the substance is known to be used as a plasticiser. Typical applications identified in literature include use in materials such as (Wypych, 2004):

- Ethylene Vinyl Acetate (EVA) copolymers;
- polylactides (e.g. biodegradable shrink films);
- PVC (e.g. interlayer of laminated glazing compounds);
- adhesives and sealants (e.g. automotive laminates); and
- indirect additives to food (e.g. plasticisers in polymeric articles, surface lubricants used in the manufacture of metallic articles).

Several more patents have been identified in which IDP is used for cosmetic formulations.

Comparison against key technical feasibility and selection criteria

Trials with the substance and perceived overall technical suitability: this information is presented in the Confidential Annex.

Comparison against the key technical feasibility and selection criteria: this information is presented in the Confidential Annex.

4.11.3 Reduction of overall risk due to transition to the alternative

4.11.3.1 Hazard information

Information on the hazards of IDP has been sought from a variety of sources, given that the substance has not been registered in the EU and information from a CSR is not yet available. The information collected from German and Canadian sources is summarised in Table 4.84.

Table 4.84: Hazard information on IDP

Database	Parameter	Value
German Federal Environmental Agency List of Substances which are Hazardous to Water	Hazard class (Note: there are three water hazard classes (WGK): 1: low hazard to waters 2: hazard to waters 3: severe hazard to waters)	1
Canada Domestic Substance List (DSL) (2007)	Substance category	Organics
	Bioaccumulative	No (rationale: Category)
	Persistent	No (rationale: QSAR)
	Inherently Toxic to Aquatic Organisms	Uncertain
	Meets CEPA Categorization Criteria	No
	Meets Environmental Criteria for Categorization	No
	Meets Human Health Criteria	No
	DSL Quantity range (tonnes/year)	>1 to 1,000
Sources: *German Federal Environmental Agency Internet site:* http://webrigoletto.uba.de/rigoletto/public/searchDetail.do?kennummer=4322 *OECD Internet site:* http://webnet.oecd.org/ccrweb/ChemicalDetails.aspx?ChemicalID=1DCA1848-DD37-4CD9-A304-F167461FC4DF *US EPA ACToR Internet site:* http://actor.epa.gov/actor/GenericChemical?casrn=109-32-0 *Chemical Carcinogenesis Research Information System Internet site:* http://toxnet.nlm.nih.gov/cgi-bin/sis/search/r?dbs+ccris:@term+@rn+85-98-3		

Additional data, as presented in Table 4.85 on the properties of the substance, are also available from the Canada Domestic Substance List referred to above. These can be seen to be largely based on estimates and predictions derived from a number of (Q)SAR systems rather than being based on experimental findings per se.

Table 4.85: Ecological data supporting decisions of Environment Canada on IDP

Parameter	Value
Persistence	
Media of concern leading to Categorization	Soil
Experimental biodegradation half-life (days)	Not Available
Predicted ultimate degradation half-life (days)	15
Biodegradation (by MITI)	0.911
Biodegradation (by TOPKAT)	1
EPI Predicted hydrolysis half-life (days)	3.32×10^3
Ozone reaction half-life (days) (predicted by EPI)	999
Atmospheric oxidation half-life (days) (predicted by EPI)	0.4912
Bioaccumulation	
$LogK_{ow}$(predicted by KowWin)	8.16
Log BAF T2MTL (predicted by Gobas)	6.480
Log BCF 5% T2LTL (predicted by Gobas)	3.952
Log BCF max (predicted by OASIS)	3.949
Log BCF (predicted by BCFWIN)	1.725
Source: OECD Internet site: http://webnet.oecd.org/ccrweb/ChemicalDetails.aspx?ChemicalID=1DCA1848-DD37-4CD9-A304-F167461FC4DF	

No other information has been identified. Kaplan & Kaplan (1985) suggest that, although no toxicological information on the substance was available at that time, it was presumed to be non-toxic and that biodegradation by microbial and mammalian esterases would be expected.

Given the very limited dataset on the hazardous properties of IDP publically available, QSAR models (OECD QSAR toolbox and FDA EKDB models) were employed to derive additional insight into the potential mammalian and ecotoxicological profile of this substance. The outputs of the modelling (and associated references) are presented in Table 4.86, overleaf.

Based on all available information, the hazard profile of this substance may be summarised as follows.

Mammalian hazard profile

Acute toxicity: no information is available on the acute toxicity of IDP. However, as noted in Table 4.84, IDP is reported not to meet the Human Health Criteria under the Canada Domestic Substance List.

Repeat dose toxicity: no information is available on the repeat dose toxicity of IDP. However, as noted in Table 4.84, IDP is reported not to meet the Human Health Criteria under the Canada Domestic Substance List.

Irritancy and sensitisation: no robust predictions were possible using the OECD QSAR models with regard to either skin or eye irritancy, though the estimates generated were negative. A prediction for dermal sensitisation considered valid was found to be negative suggesting that there is no basis for concern with regard to this endpoint. On the other hand, publicly available Safety Data Sheets allude to possible irritation of the respiratory tract or allergic skin reactions as a result of exposure to IDP[44].

Genotoxicity and carcinogenicity: predictions from QSAR modelling provided no basis for concern regarding the in vitro or in vivo mutagenic potential of the substance. Although two equivocal predictions for in vitro clastogenicity in mammalian cells (hamster and mouse) were identified, a QSAR prediction for an in vivo mouse micronucleus assay was negative. Hence, little concern is raised with regard to the genetic toxicity of IDP.

Similarly, a series of predictions relating to carcinogenicity from QSAR models operating within their domains failed to raise concern with regard to the substance's carcinogenic potential.

Reproductive and developmental toxicity: no information is available as to the reproductive toxicity of the substance. A QSAR prediction based on the TERIS database suggests that the substance is not a developmental toxin.

Other toxicities: QSAR predictions of the substance's ability to interact with proteins or with the oestrogen receptor and receptor gene, were negative. In contrast, an apparently robust FDA EKDB prediction indicated that IDP may interact with the androgen receptor, raising some concern with regard to its endocrine disrupter potential.

[44] See Safety Data Sheet here: http://images.www.mpbio.com/docs/msds/ansi/en/MP_MSDS_201821_EN_ANSI.pdf (accessed on 15 February 2013).

Table 4.86: Human health and environmental hazard profile for IDP

Hazard endpoint		Finding	Data source	Study design	Assessed robustness/Comment
Toxicokinetics		93.5%	OECD QSAR	QSAR prediction of human intestinal absorption by Multicase expert system	Result reported to be undefined with regard to domain applicability, hence considered of uncertain reliability
Irritation	Skin irritation/corrosion	Not irritating or corrosive to skin	OECD QSAR	QSAR prediction for severe skin irritation, by Bundesinstitut für Risikobewertung (BfR) skin irritation/corrosion	Result reported to be undefined with regard to domain applicability, hence considered of doubtful reliability
		Not irritating or corrosive to skin	OECD QSAR	QSAR prediction for undefined endpoint, by BfR skin irritation/corrosion	Result reported to be undefined with regard to domain applicability, hence considered of doubtful reliability
	Eye irritation	Not irritating or corrosive to eye	OECD QSAR	QSAR prediction by BfR eye irritation/corrosion	Result reported to be undefined with regard to domain applicability, hence considered of uncertain reliability
Sensitisation	In vivo - Skin sensitisation	Negative	OECD QSAR	QSAR prediction by skin sensitisation, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
Genetic toxicity	In vitro - Mutagenicity	Negative	OECD QSAR	QSAR prediction for Ames test (*S. typhimurium* ,strain and metabolic activation status undefined), from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Negative	OECD QSAR	QSAR prediction for unscheduled DNA-synthesis in rat cells, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Negative	OECD QSAR	QSAR prediction for DNA reactivity based on Ashby fragments, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Negative	OECD QSAR	QSAR prediction for mouse COMET Assay, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Negative	OECD QSAR	QSAR prediction for unscheduled DNA repair in an in vitro Syrian Hamster Embryo cell assay from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Negative	OECD QSAR	QSAR prediction for unscheduled DMA repair in an in vitro mouse bone marrow assay from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
	In vitro – Chromosomal effect	Equivocal	OECD QSAR	QSAR prediction for chromosomal aberration in an in vitro COMET assay in mouse cells, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable

Hazard endpoint		Finding	Data source	Study design	Assessed robustness/Comment
		Equivocal	OECD QSAR	QSAR prediction for chromosome aberration in a Chinese Hamster Ovary (CHO) assay, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
	In vivo - Mutagenicity	Negative	OECD QSAR	QSAR prediction for Drosophila sex-linked recessive lethal test, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Negative	OECD QSAR	QSAR prediction for rodent dominant lethal assay, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
	In vivo – Chromosomal effect	Negative	OECD QSAR	QSAR prediction for mouse micronucleus assay, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
Carcinogenicity		Negative	OECD QSAR	QSAR prediction based on FDA Cancer Female Mouse, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Negative	OECD QSAR	QSAR prediction based on FDA Cancer Male Mouse, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Negative	OECD QSAR	QSAR prediction based on Mouse lymphoma, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		TD_{50} = 1000 mg/kg/day	OECD QSAR	QSAR prediction by mouse Carcinogenic Potency Database (CPDB), from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Negative	OECD QSAR	QSAR prediction based on FDA Cancer Female Rat, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		Negative	OECD QSAR	QSAR prediction based on FDA Cancer Male Rat, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		TD_{50} = 1000 mg/kg/day	OECD QSAR	QSAR prediction by rat Carcinogenic Potency Database (CPDB), from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
Toxicity to reproduction		No information			
Developmental toxicity / Teratogenicity		Negative	OECD QSAR	QSAR prediction based on FDA Teratogen Information System (TERIS), from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
Other toxic endpoints	Protein binding potential	No alert found	OECD QSAR	QSAR toolbox prediction	No information on robustness of prediction
		No alert found	OECD QSAR	QSAR prediction by OASIS	No information on robustness of prediction
	Androgen receptor binding activity	Log RBA = -10000 to -2.73	FDA EKDB model	QSAR prediction that IDP may show AR binding potential, based on similarity (0.94-1) to di(2-ethylhexyl) adipate, dibutyl adipate and di-i-butyl adipate	Reported to be within QSAR domain, hence considered acceptable

Hazard endpoint		Finding	Data source	Study design	Assessed robustness/Comment
	Estrogen receptor binding activity	ERBA = Negative	OECD QSAR	QSAR prediction by estrogen receptor relative binding activity, from Danish EPA Database	Reported to be within QSAR domain, hence considered acceptable
		ERB = 10%	OECD QSAR	QSAR prediction by estrogen receptor binding activity (Multicase)	Reported to be outside of QSAR domain, hence considered of doubtful reliability
		Non binder, non-cyclic structure	OECD QSAR	QSAR prediction	No indication identified that model was operating outside of its operational limits
		Log RBA = -10000	FDA EKDB model	QSAR prediction that IDP is inactive in ER binding, based on similarity to di(2-ethylhexyl) adipate, cineole and suberic acid	Reported to be within QSAR domain, hence considered acceptable
	Estrogen receptor gene activation	Log RP = -10000	FDA EKDB model	QSAR prediction that IDP is inactive for the ER gene, based on similarity to di(2-ethylhexyl) adipate, dibutyl adipate and di-i-butyl adipate	Reported to be within QSAR domain, hence considered acceptable
Aquatic Toxicity	Taxa unspecified	Growth EC_{50}=0.106 µg/L	OECD QSAR	QSAR estimation of growth by uTOX (Multicase)	Reported to be within QSAR domain, hence considered acceptable
	Taxa unspecified	Immobilisation EC_{50} = 0.106 µg/L	OECD QSAR	QSAR estimation of immobilisation endpoint by uTOX (Multicase)	Reported to be within QSAR domain, hence considered acceptable
	Taxa unspecified	Mortality EC_{50} = 0.106 µg/L	OECD QSAR	QSAR estimation for EC50 by uTOX (Multicase)	Reported to be within QSAR domain, hence considered acceptable
	Bacteria	Mortality EC_{50} = 0.106 µg/L (5 minutes)	OECD QSAR	QSAR prediction for *V. Fischeri*, by uTOX (Multicase)	Reported to be within QSAR domain, hence considered acceptable
Sources: *OECD QSAR Data obtained using OECD QSAR Toolbox at Internet site:* *http://www.oecd.org/chemicalsafety/assessmentofchemicals/theoecdqsartoolbox.htm#Download_qsar_application_toolbox* *FDA EKDB data obtained using FDA EKDB Database at Internet site:* *http://www.fda.gov/ScienceResearch/BioinformaticsTools/EndocrineDisruptorKnowledgebase/default.htm*					

Environmental fate and behaviour and ecotoxicology

In the German Federal Environmental Agency List of Substances which are Hazardous to Water, IDP is given a hazard class of 1 (i.e. low hazard to waters). Information from the Canadian Domestic Substances also suggests the substance is neither persistent nor bioaccumulative based on QSAR modelling, and that it does not meet the Canadian Environmental Criteria for categorisation. Reassurance as to its limited aqueous solubility is given by a report for the United States Army NATICK Research and Development Center (Kaplan & Kaplan, 1985), which indicates that IDP shows negligible water solubility (<2 mg/L). Although suggesting it is relatively stable, the authors also note that it is susceptible to metabolism by esterases of microbial and mammalian origin, followed by biodegradation via β–oxidation.

No other published ecotoxicity information was identified. A series of QSAR predictions of its ecotoxic potential, drawn from a single source, apparently indicate a high acute toxic potential in aquatic taxa, although the taxa affected in this way are not clearly identified (see Table 4.86). In this respect, it is noted that the 'uncertain' finding by the Canadian authorities with regard to its inherent toxicity to aquatic organisms appears to reflect the absence of any information on relevant endpoints. Therefore, it appears that further research to better establish the aquatic toxic potential of the substance may be appropriate before its suitability as a potentially less toxic alternative can be fully assessed.

4.11.3.2 Comparison of hazards

There is a dearth of experimental data on this substance and only limited insight into some aspects of its toxicity is available using QSAR modelling. Hence, any assessment of its overall human health or ecotoxic potential should be regarded as tentative and subject to a considerable degree of uncertainty. In particular, there is a lack of even basic understanding of its acute, repeat dose or reproductive toxic potential.

Nonetheless, based on the limited available information, there appears to be little concern with regard to its genotoxicity or carcinogenicity, and it does not appear to raise major concerns with regard to its environmental fate or behaviour. There are some (isolated) suggestions that the substance may cause lung irritation and skin effects but the validity of such warning has not been possible to confirm. Also, there is a potential basis for some concern with regard to its predicted potential to interact with the androgen receptor, suggesting that there would be a need to establish its potential to cause endocrine disruption and, by inference, to affect the reproductive or developmental functions of organisms before any conclusion could be reached with regard to the overall risks posed to humans. Finally, there is an indication, in the light of the limited QSAR modelling undertaken, that further investigation of its aquatic toxic potential may be appropriate.

Table 4.87 summarises our tentative understanding of the hazard profile of IDP, in comparison of that established for DBP. It should, however, be noted that there remains significant gaps in understanding with regard to critical human health endpoints.

Table 4.87: Hazard comparison of DBP with IDP

Hazard endpoint	IDP	DBP
Human health		
Acute toxicity		
Irritancy	Uncertain (concerns regarding skin, eye and respiratory tract)	
Repeat dose		Toxic
STOT		Liver, kidney, testes
Reproductive toxicity		1B (male fertility)
Developmental toxicity		1B (males)
Carcinogenicity		Data are insufficient to determine the carcinogenic potential. No evidence of carcinogenicity is available. The CSR assumes that the substance is not a carcinogen
Environment		
Aquatic	Uncertain	Very toxic
Other		
Other issues	Possible endocrine activity (QSAR prediction of androgen receptor interaction potential)	
Note: grey cells indicate areas where no relevant information is available		

4.11.4 Economic feasibility

DEZA does not manufacture IDP as it is unfamiliar with the technology and process parameters required for its production but, primarily, due to a lack of demand for the substance by the DUs. Although IDP is an ester, it is currently not included in DEZA's product portfolio.

Importantly, due to the unproven technical feasibility of the substance from the perspective of DUs, it is unclear whether any of them would actually use IDP as a substitute for DBP. Moreover, even if IDP would prove to be technically feasible for some of the applicant's customers, the volume of current sales of DBP to propellant manufacturers that could be substituted with IDP would likely only be very modest, due to the fact that IDP could only be used as a substitute plasticiser, thus would be potentially suitable to replace <<10% of the tonnage of DBP currently used by the applicant's DUs.

As explained for other alternative substances, a certain minimum tonnage of ester has to be manufactured before the economics of production become viable; the volume of current sales of DBP to propellant manufacturers cannot justify the investment cost associated with the setting up of a new production line for IDP, especially since DEZA would face strong competition from established suppliers of the substance.

This alternative substance cannot be considered economically feasible for the applicant. Under a refused Authorisation, sales of DBP to propellant manufacturers would be lost and could only be replaced by a much more modest level of IDP sales, if any at all.

Additional confidential information is presented in: AoA Confidential Annex DBP Propellants DEZA.pdf, Section 4.1.3

4.11.5 Availability

4.11.5.1 Current and projected availability

Availability for the applicant

As discussed above, IDP is manufactured using technology that is unknown to DEZA and its compatibility with the current esterification plant is uncertain as is uncertain the accessibility to the acid precursor to IDP. The applicant cannot manufacture IDP at present.

Availability for the downstream users

From the perspective of the DUs, the market availability of IDP is given in Table 4.88.

Table 4.88: Market availability of IDP

Alternative	Data availability	Market availability from the perspective of the downstream users
IDP	Very limited	Uncertain availability Not REACH registered

4.11.5.2 Actions required for improving availability

Availability for the applicant

For IDP to become available to the applicant the ability of the existing esterification plant to manufacture IDP at sufficient quantities, if there a market incentive for doing so.

The Confidential Annex to this AoA explains the tasks that the applicant would have to undertake in researching, trialling and starting the production of IDP at their plant. The time that would be required for such production to be initiated at the industrial scale would extend beyond the Sunset Date for the Authorisation of DBP even if DEZA started the process of researching the production of IDP as soon as this AfA was submitted.

The conclusion is that the availability of the substance for the applicant would be unlikely to improve in the foreseeable future.

Additional confidential information is presented in: AoA Confidential Annex DBP Propellants DEZA.pdf, Section 4.1.4

Availability for the downstream users

It is unclear whether and how the availability of IDP for the DUs may change in the future.

4.11.6 Conclusion on suitability and availability of IDP

4.11.6.1 Technical suitability

The substance is not available to the applicant and it is manufactured with raw materials to which the applicant has no access, therefore it may not be considered technically feasible.

From the perspective of DUs, IDP might potentially be usable as a plasticiser, but not as a moderant. As such, it can be suitable only for a small percentage of the relevant products of the identified DUs. The assessment of technical suitability made by some consultees is based on assumptions rather than firm knowledge of the technical advantages and disadvantages of the substance.

In summary, a meaningful comparison of technical suitability to that of DBP cannot be provided given the virtually non-existent experience of the propellant manufacturers with the substance.

4.11.6.2 Reduction of overall risk

Based on the available information, there appears to be little concern with regard to potential genotoxicity or carcinogenicity of IDP and it does not appear to pose major concerns with regard to the environmental fate and behaviour. It must be highlighted, however, that the substance raises potential concerns with regard to irritation, sensitisation and endocrine status, given that it was noted that it may be active with the androgen receptor, and in the absence of any data on repeat dose or reproductive toxicity, the possible significance of these findings is difficult to interpret, but is of some concern. As the risks from exposure to DBP from its use in the formulation and subsequent use of propellants are adequately controlled, the use of IDP would not result in discernible benefits to DUs' workers' health.

4.11.6.3 Economic feasibility

Given the uncertain uptake of IDP by DUs, the applicant's lack of knowledge over the production conditions and the need to ensure that a minimum sales tonnage must be achieved before the production of a new ester compound can be profitable, IDP cannot be considered economically feasible for the applicant. This is particularly true because the amount of DBP currently used as a plasticiser in propellants is considerably low.

4.11.6.4 Availability

From the perspective of the applicant, the substance is not available to him. Moreover, the future availability of the substance is unlikely to change; the quantity of IDP that would be sold by DEZA is too small to justify the expense of setting up and operating a new production line for IDP.

Key point 19

IDP appears to perform poorly against DBP and may only be considered a potential substitute plasticiser. The experience of propellant manufacturers with the substance is non-existent. Information on its hazard profile is scant and questions may be raised in relation to irritation, sensitisation and endocrine status, while risks from DBP are already adequately controlled. Its economic feasibility and availability are unacceptable to the applicant

5 OVERALL CONCLUSIONS ON SUITABILITY AND AVAILABILITY OF POSSIBLE ALTERNATIVES FOR PROPELLANTS

5.1 Conclusions on the technical suitability of possible alternatives

In the preparation of this AoA, a wide range of potential alternatives was looked into: non-energetic alternative substances, energetic alternative substances and alternative propellant technologies. Of these, only non-energetic chemical substances can be of relevance to the applicant and the focus of this AoA has been on them, as explained in Section 3.1 above. The remaining theoretical alternative solutions for DUs are discussed in Annex 7 of the SEA, where it is shown that they are not technically and economically feasible solutions for the DUs.

Among the 10 potential alternative substances that have been shortlisted as the most relevant to the manufacture of nitrocellulose-based propellants, the only one that is technically feasible for the applicant is DEHA, as it is already produced by the applicant in sufficient quantities. However, DEHA is a known plasticiser and as such could only be feasibly used as a substitute for DBP in a small minority of cases. Table 2.1 explains that <<10% of the sales/consumption of DBP in the field of propellants relates to DBP's functionality as a plasticiser (as opposed to a moderant of the burning rate).

No other potential alternative substance is manufactured by the applicant and their esterification plant is incapable of manufacturing urea alternatives, i.e. centralites and Akardites. For all nine selected potential alternative substances, issues would arise with regard to:

- the availability of and/or access to precursors;
- the lack of knowledge of the parameters and conditions of the reactions involved; and
- the very modest foreseeable demand for any of the potential alternative substances, which could not justify the investment that would be required in securing the precursors and developing knowledge of and implementing the required manufacturing technology.

A summary of our findings with regard to the technical suitability of the selected potential alternative substances is given in Table 5.1. This Table focuses on the technical feasibility of the potential alternative substances from the perspective of the applicant. An expanded version of this Table is provided in the Confidential Annex (Table 5.1), in which technical feasibility issues for the DUs are also summarised.

Table 5.1: Overview of comparison of technical suitability of potential alternatives to DBP

Alternative	Data availability on potential for replacing DBP	Potentially suitable as a…		Technical suitability to applicant
		Moderant	Plasticiser	
Methyl centralite	Limited	✓	×	- Not manufactured by applicant - No access to precursors - Use of precursors would be very problematic for technical and safety reasons - Existing esterification plant cannot manufacture urea derivatives **Conclusion: Not technically feasible for the applicant**

Alternative	Data availability on potential for replacing DBP	Potentially suitable as a…		Technical suitability to applicant
		Moderant	Plasticiser	
Ethyl centralite	Limited	✓	×	- Not manufactured by applicant - No access to precursors - Use of precursors would be very problematic for technical and safety reasons - Existing esterification plant cannot manufacture urea derivatives **Conclusion: Not technically feasible for the applicant**
Akardite I	Very limited	✓	×	- Not manufactured by applicant - No access to precursors - Use of precursors would be very problematic for technical and safety reasons - Existing esterification plant cannot manufacture urea derivatives **Conclusion: Not technically feasible for the applicant**
Akardite II	Limited	✓	×	- Not manufactured by applicant - No access to precursors - Use of precursors would be problematic - Existing esterification plant cannot manufacture urea derivatives **Conclusion: Not technically feasible for the applicant**
Akardite III	Very limited	✓	×	- Not manufactured by applicant - No access to precursors - Use of precursors would be problematic - Existing esterification plant cannot manufacture urea derivatives **Conclusion: Not technically feasible for the applicant**
DEHA	Limited	×	✓	- Technology available to applicant - Currently in production **Conclusion: Technically feasible for the applicant, but infeasible for the vast majority of propellants manufactured by the DUs (especially small calibre ammunition propellants)**
ATBC	Limited	✓	✓	- Not manufactured by applicant - Availability of precursors uncertain - Conditions and parameters of esterification currently uncertain - Possible purity issues - Plant conversion would be complex and costly **Conclusion: Not technically feasible for the applicant**
TBC	Limited	✓	✓	- Not manufactured by applicant - Availability of precursors uncertain - Conditions and parameters of esterification currently uncertain **Conclusion: Not technically feasible for the applicant**

Alternative	Data availability on potential for replacing DBP	Potentially suitable as a…		Technical suitability to applicant
		Moderant	Plasticiser	
DOZ	Very limited	×	✓	- Not manufactured by applicant - Availability of precursors uncertain - Conditions and parameters of esterification currently uncertain **Conclusion: Not technically feasible for the applicant**
IDP	Very limited	×	✓	- Not manufactured by applicant - Availability of precursors uncertain - Conditions and parameters of esterification currently uncertain **Conclusion: Not technically feasible for the applicant**

Additional confidential information is presented in: AoA Confidential Annex DBP Propellants DEZA.pdf, Section 5.1

5.2 Conclusions on the reduction of risks that possible alternatives may deliver

In relation to the comparison of hazards and risks between DBP and the selected potential alternative substances, a summary of findings by substance is presented in Table 5.2. Additionally, Table 5.3 compares all potential alternative substances amongst themselves and highlights the potential concerns that each one of the selected alternatives may raise, as detailed in the Confidential Annex to the AoA. The key conclusions are as follows:

- risks to the employees of the applicant's DUs (propellant and ammunition manufacturers) are currently adequately controlled below the effect threshold for DBP. Therefore, the substitution of DBP by any alternative substance would not confer any discernible benefit to these workers' health. No risk to the user of propellant or ammunition or to the environment is envisaged from the use of the ammunition that contains the DBP-based propellant;
- when the hazard profiles of alternatives are compared to that of DBP, it appears that the alternatives generally have a more benign profile. For the endpoint for which DBP was listed on Annex XIV of the REACH Regulation (reproductive toxicity), none of the selected potential alternative substances appears to raise any concern, with the exception of DEHA, for which there is some concern, in part because of its structural similarity to DEHP;
- concerns may exist for the selected alternatives with regard to acute toxicity (generally low), irritancy (inhalation, skin and eye are affected by the majority of the potential alternatives), repeat dose toxicity (ATBC), and aquatic toxicity (the majority of the potential alternatives). Tentative concerns on the endocrine disruption potential of some (DOZ and IDP) have also been raised in the Confidential Annex; and
- the majority of the selected alternatives have not been adequately researched and many of the preliminary conclusions reached in this AoA are based on alternative testing approaches. For some of the potential alternatives (Akardite I & III and IDP) the lack of information renders any comparison to DBP extremely uncertain.

Table 5.2: Overview of hazards/risks of potential alternative substances to DBP

Alternative	Data availability	Comparison of hazard/risk profile to DBP	
		Overall comparison	**Areas of concern**
Methyl centralite	Limited	Probably safer than DBP	- Issues with carcinogenic decomposition products in nitrocellulose-based propellants - Concerns about irritancy and effects on the aquatic environment - Majority of information on its key toxicological and eco-toxicological properties is based on alternative texting approaches - Less thoroughly investigated than DBP - Concerns about safety issues raised by precursors
Ethyl centralite	Reasonable (but still gaps)	Possibly safer than DBP	- Issues with carcinogenic decomposition products in nitrocellulose-based propellants - Uncertainty regarding repeat dose toxicity - Concerns about irritancy and effects on the aquatic environment - Less thoroughly investigated than DBP - Concerns about safety issues raised by precursors
Akardite I	Very limited	Probably safer than DBP	- Issues with carcinogenic decomposition products, but less problematic than centralites - Concerns about acute toxicity, gap in understanding of its toxic profile in relation to repeat dose toxicity and reproductive toxicity - Unlikely to constitute the same level of environmental hazard as DBP - Less thoroughly investigated than DBP - Concerns about safety issues raised by precursors
Akardite II	Very limited	Probably safer than DBP	- Issues with carcinogenic decomposition products, but less problematic than centralites - Concerns about eye irritation - Limited degree of concern with regard to potential for genotoxicity in mammalian species - Possible concern with regard to its acute aquatic toxicity - Less thoroughly investigated than DBP - Concerns about safety issues raised by precursors
Akardite III	Very limited	Lack of information; comparison not possible	- Issues with carcinogenic decomposition products, but less problematic than centralites - Some concerns regarding toxicity and ecotoxicity when assessed using alternative testing approaches - Far less thoroughly investigated than DBP, significant information gaps - Concerns about safety issues raised by precursors
DEHA	Good (CSR)	Probably safer than DBP	- Higher DNEL values for workers than DBP - Concerns about reproductive toxicity - Recently placed on CoRAP in respect to its suspected CMR properties - Does not constitute an environmental hazard even at aqueous concentration above its limit of solubility
ATBC	Good (CSR*)	Safer than DBP	- Higher DNEL values for workers than DBP have been proposed, though robustness uncertain - Potential issues with aquatic toxicity and bioaccumulation potential
TBC	Reasonable (CSR, but still gaps)	Probably safer than DBP	- Classification for aquatic toxicity and uncertainty regarding environmental behaviour - Acute effects on eye exposure - Less thoroughly investigated than DBP
DOZ	Reasonably good (SIDS, CSR)	Safer than DBP	- No specific concern identified, no DNELs developed - Some concern regarding androgen receptor interaction potential when assessed using alternative testing approaches, and with regard to ambiguous sensitisation data
IDP	Very limited	Lack of information; comparison not possible	- Potential concern regarding irritation and sensitisation - Uncertainty over aquatic toxicity - Some concern regarding androgen receptor interaction potential when assessed using alternative testing approaches - Far less thoroughly investigated than DBP, significant information gaps
** No longer available on ECHA Dissemination Portal (as of 5 July 2013)*			

Table 5.3: Potential human health and environmental concerns for the potential alternative substances

	DBP	Methyl centralite	Ethyl centralite	Akardite I	Akardite II	Akardite III	DEHA	ATBC	TBC	DOZ	IDP
Human health											
Acute toxicity	Very low	Slight (oral)	Slight (oral)	Slight/ Moderate (oral, inh)	Slight	No data			Slight (oral, inh)	Very low (oral)	No data
Irritancy		Inhalation	Inhalation	Skin (?)	Ocular		Skin, inhalation	Eye	Ocular, skin, inhalation, GI, resp.	Weak (Skin, eye)	Uncertain (ocular, skin, resp.)
Sensitisation		No data	No data	No data	No data	No data				Uncertain	
Repeat dose toxicity	Toxic	No data	Uncertain	No data	No data	No data	Toxic	Toxic	No data		No data
STOT	Liver; kidney; testes		Liver, kidney, ovary & uterus (?)				Kidney, liver, ovary	Liver kidney			
Reproductive toxicity	1B (male fertility)	No data	No data	No data	No data	No data	Toxic		No data		No data
Develop-mental toxicity	1B (Males)					No data	Toxic				
Genotoxicity					Uncertain						
Carcino-genicity	No data						Yes (mouse)				
Ecotoxicity											
Aquatic	Very toxic	Toxic	Toxic (long-lasting)		Uncertain	Uncertain	Conflicting evidence	Uncertain	Very toxic (acute)		Uncertain
Terrestrial											
STW/bacterial											
Secondary poisoning											
Other		Degrada-tion products	Degrada-tion products	Degrada-tion products	Degrada-tion products	Degrada-tion products				Androgen receptor interaction	Androgen receptor interaction

5.3 Conclusions on the economic feasibility of possible alternatives

Only one of the potential alternatives is currently manufactured by the applicant, DEHA. For this, it has been shown that only a minor percentage of the current sales of DBP in the field of propellants would be possible to be replaced with sales of DEHA. Therefore, this substance cannot be considered economically feasible for the applicant.

Among the remaining nine selected potential alternative substances, five are urea derivatives, which the applicant cannot manufacture in their existing plant. Conversion to one of those would be very long and exceedingly costly when considering the lack of certainty on the technical feasibility of each of these substances for the DUs, as well as the very modest tonnage that DEZA would foreseeably be able to successfully sell to their customers.

For the remaining four potential alternative substances, a costly plant conversion would probably not be required; however, the development of expertise in their manufacture would take a considerable time and the amount that the applicant would potentially be able to sell would be too low to justify the associated expenditure in R&D and investment (particularly for DOZ and IDP which might only act as substitute plasticisers). As above, the technical feasibility of these four substances is yet to be confirmed through DUs' R&D work, which is still on-going.

As summary of findings on the issue of economic feasibility is given in Table 5.4. The SEA further discusses the costs for DUs, including users of ammunition and operators of military and civilian aircraft, associated with the use of alternatives to DBP.

Table 5.4: Overview of economic feasibility of potential alternative substances to DBP

	Lack of access to technology and expertise	Plant incompatibility with alternative and its precursors	New production plant required	Conversion timeline	Foreseeable sales volume	Competition status
Methyl centralite	✓	✓	✓	Very long (years)	Low	Established
Ethyl centralite	✓	✓	✓	Very long (years)	Low	Established
Akardite I	✓	✓	✓	Very long (years)	Low	Uncertain
Akardite II	✓	✓	✓	Very long (years)	Low	Established
Akardite III	✓	✓	✓	Very long (years)	Low	Uncertain
DEHA	×	×	×	Zero	Very low (<<10% of DBP sales)	Applicant has established presence but competitors exist
ATBC	✓	×	×	Long (beyond Sunset Date)	Low	Established
TBC	✓	×	×	Long (beyond Sunset Date)	Low	Established
DOZ	✓	×	×	Long (beyond Sunset Date)	Very low (<<10% of DBP sales)	Established
IDP	✓	×	×	Long (beyond Sunset Date)	Very low (<<10% of DBP sales)	Uncertain

5.4 Conclusions on the market availability of possible alternatives

A summary of our findings on the market availability of the selected potential alternative substances is presented in Table 5.5, overleaf. Of all alternatives, only one, DEHA, is available to the applicant. Phenyl ureas cannot become available without a new production facility and alternative esters (other than DEHA) would require lengthy testing and development of the required knowledge and technology before production at the industrial scale becomes feasible. The current demand for DBP in the explosives sector is too low to make such a proposition financially viable and attractive. With regard to the applicant's access to the precursors to the alternatives, the Confidential Annex (Section 4.1.2.2) explains in detail the issues that DEZA would face. The summary given in Table 5.5 would suggest that only for alternative esters availability of precursors might be acceptable.

From the perspective of DUs, the majority of potential alternatives are probably accompanied by good market availability (in any case, the tonnage of alternatives that would be required is rather modest), although uncertainties do exist for some of them, namely Akardite I, Akardite III and IDP. Half of the selected potential alternative substances are yet to be registered under REACH.

5.5 Overall conclusion

From the perspective of the applicant, none of the selected potential alternative substances can be considered suitable to replace DBP. The only alternative which the applicant can place on the market (DEHA) would only be a potentially feasible plasticiser for <<10% of the total current usage of DBP in propellants. Economically, this cannot be considered feasible, as DEZA would likely lose its entire propellant-related turnover. It is recognised that in terms of hazard potential, the available information would indicate that the considered potential alternative substances do not raise concerns regarding their reproductive toxicity potential. Yet, many of the potential alternatives are far less researched than DBP and could still be accompanied by concerns of their own, both in relation to human health and the environment. It is important to note that, as shown in the CSR, exposure to DBP is kept below the effect threshold during the formulation and use of propellants and, as such, no discernible benefit to workers' health would arise from the use of any of the selected potential alternative substances.

5.6 Planned future Research and Development for the substitution of DBP

5.6.1 Research and Development for ammunition propellants

The applicant is not in a position to undertake extensive R&D for the development of a suitable substitute for DBP in propellants. The quantity of DBP currently sold to propellant manufacturers is too small to justify major investment in the investigation and introduction of new technology that would allow the manufacture of alternative substances other than DEHA, which is already produced.

On the other hand, propellant manufacturers have provided information on the R&D they have undertaken so far and their plans for future R&D aimed at investigating and developing technically and economically feasible alternatives for DBP in ammunition propellants. The general steps taken in the investigation and implementation of an alternative moderant or plasticiser include the following, as shown in Table 3.2:

Table 5.5: Overview of comparison of the market availability of potential alternatives to DBP

Potential alternative substance	Data availability	Market availability from the perspective of the applicant			Market availability from the perspective of the downstream user	
		Availability of/access to technology	Availability of/access to precursors		Market status	REACH registration status
			Acid/carbonyl	Alcohol/amine		
Methyl centralite	Limited	Not available as its manufacture is based on technology not available to the applicant; **impossible to manufacture** with existing plant. Future production is not envisaged due to low foreseen demand	×	?	Generally available	Not REACH registered
Ethyl centralite	Limited		×	?	Generally available	Registered under REACH
Akardite I	Very limited		?	✓	Potentially available. Some consultees have experienced difficulty in sourcing the substance	Not REACH registered
Akardite II	Very limited		?	?	Generally available	Not REACH registered
Akardite III	Very limited		?	?	Uncertain availability. Some consultees have experienced difficulty in sourcing the substance	Not REACH registered
DEHA	Good	Available – currently manufactured at sufficient tonnage	✓	✓	Available on the market	Registered under REACH
ATBC	Good	Not available as its manufacture is based on technology not available to the applicant. Compatibility with existing plant is uncertain; testing and trialling are required. Future production is not envisaged due to low foreseen demand	(✓)	✓	Available on the market	Registered under REACH (assumed)
TBC	Limited		✓	✓	Available on the market	Not REACH registered
DOZ	Very limited		?	✓	Available on the market	Registered under REACH
IDP	Very limited		?	×	Uncertain availability	Not REACH registered

- literature review and internal discussion;
- assessment of the compatibility of candidate substitutes;
- laboratory scale testing;
- pilot plant scale testing; and
- industrial scale testing.

Propellant manufacturers have confirmed that they have started the investigation of potential alternatives and the progress that has been made so far varies by company, as discussed in Section 3.2.1.2. The cost of R&D that has been undertaken so far and the details of the planned future R&D activities aimed at replacing DBP are summarised in the Confidential Annex that accompanies this AoA. The Annex shows that the expected duration of planned R&D will be several years long and will entail a significant financial cost.

It is very important to note that R&D will not be the only task involved in the substitution of DBP in ammunition propellants. The reformulated propellants and the ammunition products that contain these new propellants would need to be re-qualified, as described in Section 2.3.2. The Confidential Annex provides an extensive analysis of what the duration and cost of such re-qualification be, following successful completion of the R&D phase by propellant manufacturers.

Additional confidential information is presented in: AoA Confidential Annex DBP Propellants DEZA.pdf, Section 5.6.1

5.6.2 Research and Development for aircraft pyrocartridge propellants

No R&D for the development of alternatives specifically suitable for aircraft pyrocartridges has been undertaken. The Confidential Annex discusses the challenges, duration and likely cost of any theoretical R&D for the development of a suitable functional alternative to DBP.

Additional confidential information is presented in: AoA Confidential Annex DBP Propellants DEZA.pdf, Section 5.6.2

APPENDIXES AND ANNEXES

List of references

Acros Organics. (2009). *Material Safety Data Sheet – Tributyl Citrate.* Retrieved June 9, 2012, from http://www.fishersci.com/ecomm/servlet/msdsproxy?productName=AC421442500&productDescription=TRIBUTYL+CITRATE%2C+99%2B%25+250GR&catNo=AC42144-2500&vendorId=VN00032119&storeId=10652

Aerojet-General Corporation. (1974). *Patent No. 3793097.* USA.

AFEMS. (2012). Personal communication - 24 December 2012.

Agrawal, J. (2010). *High Energy Materials: Propellants, Explosives and Pyrotechnics.* Germany: WILEY-VCH Verlag GmbH & Co.

Akhavan, J. (2011). *The Chemistry of Explosives, 3rd Edition.* United Kingdom: Royal Society of Chemistry.

Ammunition Pages. (undated). *Propellants Compositions.* Retrieved December 5, 2011, from http://www.ammunitionpages.com/download/167/propellants/20compositions.pdf

Bailey, A., & Murray, S. (2000). *Explosives, Propellants, and Pyrotechnics.* United Kingdom: Brasseys (UK) Ltd.

BAM. (2012). *Information on the Conformity Assessment Procedure according to Directive 93/15/EEC for Explosives and the Identification Number Procedure.* Retrieved October 28, 2012, from http://www.bam.de/en/service/amtl_mitteilungen/sprengstoffrecht/sprengstoffrecht_medien/merkb_explosivstoffe_en.pdf

Blachowski, T. (undated). *An Overview of the CAD/PAD Joint Program Office (JPO) Product Improvement Programs.* Retrieved December 11, 2011, from http://www.safeeurope.co.uk/media/4150/thomas%20blachowski.pdf

BlastGard. (2008). *BLASTWRAP® Terminology.* Retrieved November 5, 2012, from http://www.blastgardintl.com/td_terminology.html

Bolgar, & al. (2008). *Handbook for the Chemical Analysis of Plastic and Polymer Additives.* Boca Raton, FL: CRC Press.

CEN. (2011). *CEN Workshop 10 – European Handbook for Defence Procurement, Expert Group 2 Energetic Materials, Final Report.* Retrieved November 13, 2012, from http://www.google.co.uk/url?sa=t&rct=j&q=&esrc=s&source=web&cd=10&cad=rja&sqi=2&ved=0CFAQFjAJ&url=http%3A%2F%2Fwww.eda.europa.eu%2FEDSTAR%2FLibraries%2FStandards_Docs%2FEnergetic_Materials_-_EG_02_-_Final_report.sflb.ashx&ei=KTSiUPrnFImy0QXhiICQBg&usg=AFQ

Chassaing, A., & Finck, B. (1998). *Patent No. 5747729.* USA.

Chemcas. (2012). *Catalog of Chemical Suppliers, Buyers, Custom Synthesis Companies and Equipment Manufacturers [METHYL CENTRALITE, 213277 611-92-7]*. Retrieved May 31, 2012, from http://www.chemcas.com/msds112/cas/2773/611-92-7.asp

Chemicalland 21. (undated). *1-Methyl-3,3-Diphenylurea.* Retrieved June 5, 2012, from http://www.chemicalland21.com/specialtychem/finechem/1-METHYL-3,3-DIPHENYLUREA.htm

Chemicalland 21. (undated-b). *Tributyl Citrate.* Retrieved June 9, 2012, from http://www.chemicalland21.com/industrialchem/plasticizer/TRIBUTYL%20CITRATE.htm

Chemicalland 21. (undated-c). *Centralite II.* Retrieved June 17, 2012, from http://www.chemicalland21.com/specialtychem/finechem/CENTRALITE%20II.htm

Chemische Werke Lowi. (1978). Safety Data Sheet, Ethyl Centralite. Cordova ChemicalCo. (1977), personal communication (in Wentsel et al, 1979).

ClearSynth. (undated). *Material Safety Data Sheet - Tributyl Citrate.* Retrieved June 10, 2012, from http://www.clearsynth.com/docs/MSD-CS-U-02522.pdf

Croft, S., & Bartley, J. (2008). *The Analysis of Unfired Propellant Particles by Gas Chromatography Mass Spectrometry: A Forensic Approach.* Retrieved May 31, 2012, from http://eprints.qut.edu.au/17251/1/Shiona_Croft_Thesis.pdf

Curtis, N. (1987). *Syntheses and Characterisations of Derivatives of Ethyl Centralite.* Retrieved May 31, 2012, from http://dspace.dsto.defence.gov.au/dspace/bitstream/1947/7949/1/WSRL-0563-TR.pdf

Damse, R., & Singh, A. (2008). Evaluation of Energetic Plasticisers for Solid Gun Propellant. *Defence Science Journal, 58*(1), 86-93.

Davis. (1991). *High Production Volume (HPV) Chemicals Challenge Program: Assessment of Data Availability and Test Plan for Acetyl Tributyl Citrate (ATBC) (CAS NR 77-90-7).* Univ. Texas, Austin, TX, USA.

Doull, J., Plzak, V., & Brois, S. (1962). *A Survey of Compounds for Radiation Protection, AD 277 689.* NTIS.

Environment Canada. (2011). *Search Engine for Substances on the DSL.* Retrieved May 31, 2012, from http://www.ec.gc.ca/lcpe-cepa/eng/subs_list/DSL/DSLsearch.cfm?critSearch=CAS&critCAS=611-92-7

Finkelstein, M., & Gold, H. (1959). Toxicology of the Citric Acid Esters: Tributyl Citrate, Acetyl Tributyl Citrate, Triethyl Citrate, and Acetyl Triethyl Citrate. *Toxicology and Applied Pharmacology, 1*, 283-298.

Flanagan, J., & Haury, V. (1976). *Patent No. 3,950,196.* US.

Frys, & al. (2010). Analyses of New Nontoxic Stabilisers and Other Components in Smokeless Powders. *Journal of Energetic Materials Central European, 7*(3), 253-267.

Grote, K. (undated). *Ordnance Technology.* Retrieved December 11, 2011, from http://www.fas.org/man/dod101/sys/land/docs/ordtech.pdf

Harper, R., & Furton, K. (2007). *Biological Detection Explosives, in Counterterrorist Detection Techniques of Explosives, (ed: Yinon, J.).* UK and the Netherlands: Elsevier.

Heeb, G., Langelage, R., & Vogelsanger, B. (2008). New Stabilizers for Nitrocellulose Based Propellants, Part II (as referenced in Frys et al, 2010). *39th Int. Ann. Conf. ICT, June 24-27, 2008*, (p. 90/1). Karlsruhe, Germany.

Hirata-Koizumi, M., Takahashi, M., Matsumoto, M., Kawamura, T., Ono, A., & Hirose, A. (2012). Toxicity effects of phthalate substitute plasticizers used in toys. *Kokuritsu Iyakuhin Shokuhin Eisei Kenkyusho Hokoku, 130*, 31-42.

HSDB. (undated). *Di-2-ethylhexyl Azelate.* Retrieved JUne 14, 2012, from http://toxnet.nlm.nih.gov/cgi-bin/sis/search/r?dbs+hsdb:@term+@rn+@rel+103-24-2

Hunley, J. (1999). *The History of Solid-Propellant Rocketry: What we do and do not know.* . Retrieved December 5, 2011, from http://www.nasa.gov/centers/dryden/pdf/88635main_H-2330.pdf

IARC. (2013). *IARC Monographs on the evaluation of carcinogenic risks to humans.* Retrieved January 4, 2013, from http://monographs.iarc.fr/

Indo-Nippon Chemical Co. (undated). *Diethyl Phthalate.* Retrieved June 10, 2012, from http://www.indo-nippon.net/di-ethyl-phthalate.html

IPI. (2011). *Propellant Stabilizers.* Retrieved May 31, 2012, from http://www.islandgroup.com/military/propellant_stabilizers.php

IPI. (2011b). *Explosive and Propellant Additives.* Retrieved November 2, 2012, from http://www.islandgroup.com/military/explosives_additives.php

Johnson, W. (2002). Final Report on the Safety Assessment of Acetyl Triethyl Citrate, Acetyl Tributyl Citrate, Acetyl Trihexyl Citrate, and Acetyl Trioctyl Citrate. *Int J Toxicol., 21*(Suppl.), 1-17.

Jones, M., & Tzeng, D. (2011). *Patent No. EP 1 069 095 A1*. Europe.

Kaplan, D. L., & Kaplan, A. M. (1985). *BIOCONVERSION OF NITRAMINE PROPELLANT WASTEWATERS - TRIAMINOGUANIDINE NITRATE.* UNITED STATES ARMY NATICK RESEARCH AND DEVELOPMENT CENTER NATICK, MASSACHUSETTS 01760-50.

Kaplan, D., & Kaplan, A. (1985). *Bioconversion of Nitramine Propellant Wastewaters - Triaminoguanidine Nitrate.* Retrieved June 15, 2012, from http://www.dtic.mil/cgi-bin/GetTRDoc?AD=ADA157860

KilnFired.com. (undated). *Plasticizer Information.* Retrieved December 5, 2011, from http://www.kilnfired.com/plasticizer/encyclopedia.htm

Kirchner, D., & al. (undated). *Combustion Products of Propellants and Ammunition.* Retrieved December 5, 2011, from http://www.bordeninstitute.army.mil/published_volumes/occ_health/OHch10.pdf

Korolev, A., Arsenieva Vitvitskaya, B., Zakharova, T., & Kinzinrsky, A. (1976). Experimental Data on the Hygenic Standardization of Diphenylamine and Diphenyldiethylurate in Water Bodies. *Gig. Sanit., 5*, 21-25.

Kubota, N. (2007). *Propellants and Explosives: Thermochemical Aspects of Combustion, Second, Completely Revised and Extended Addition.* Germany: WILEY-VCH Verlag GmbH & Co.

Langlet, A. (2006). *New Ingredients in Nitrocellulose Based Propellants.* Retrieved June 5, 2012, from http://www.ep.liu.se/ecp/018/007/ecp061807.pdf

Ledgard. (2006). *The Preparatory Manual of Black Powder and Pyrotechnics.* USA: Ledgard.

Ledgard, J. (2007). *The Preparatory Manual of Explosives.* Retrieved Novermber 2, 2012, from http://books.google.co.uk/books?id=J55D3HcgPuoC

Libardi, J., Ravagnani, S., Morais, A., & Cardoso, A. (2010). Diffusion of Plasticizer in a Solid Propellant based on Hydroxyl-terminated Polybutadiene. *Polímeros, 20*(4), 241-245.

Lowell Center for Sustainable Production. (2011). *Technical Briefing - Phthalates and Their Alternatives: Health and Environmental Concerns.* Retrieved November 5, 2012, from http://www.sustainableproduction.org/downloads/PhthalateAlternatives-January2011.pdf

Maag, J., Lassen, C., Brandt, U., Kjølholt, J., Molander, L., & Hagen Mikkelsen, S. (2010). *Identification and assessment of alternatives to selected phthalates. Environmental Project No. 1341*. Danish Environmental Protection Agency .

MacPhee, C., & Ruelle, R. (1969). *Lethal Effects of 1888 Chemicals upon Four Species of Fish from Western North America.*

Mangum, M. G., Emery, J. W., & Ryder, D. D. (2002). *Patent No. EP0825074.* Europe.

Meyer, R., Koehler, J., & Homburg, A. (2002). *Explosives, Fifth Edition.* Wiley-VCH.

Meyer, R., Köhler, J., & Homburg, A. (2007). *Explosives* (Sixth, Completely Revised Edition ed.). Weinheim: Wiley-VCH Verlag GmbH.

Mirecki, & al. (2006). *Environmental Transport and Fate Process Descriptors for Propellant Compounds.* Retrieved May 30, 2012, from http://el.erdc.usace.army.mil/elpubs/pdf/trel06-7.pdf

Mortelmans, & Zeiger. (2000). *Mutat Res, 455*(1-2), 29-60.

Mukhopadhyay, R., & Datta, S. (2007). *Engineering Chemistry.* India: New Age International Publishers.

Muthiah, R., Somasundaran, U., Verghese, T., & Thomas, V. (1989). Energetics and Compatibility of Plasticizers in Composite Solid Propellants. *Def Sci J, 39*(2), 147-155.

Nichols, P. (1974). *Patent No. 3870578.* USA.

Nippon Kayaku. (2008). *Micro Gas Generator Type NKPL-2 - Material Safety Data Sheet.* Retrieved June 5, 2012, from http://dcs.hyundaidealer.com/files/resources/msds/sb17.pdf

OECD. (2006). *SIDS Document for Dioctyl Azelate.* Retrieved June 12, 2012, from http://webnet.oecd.org/Hpv/UI/handler.axd?id=0f640506-2220-4aae-b3b3-de685d164cff

Olin Winchester Ammunition. (2011). *Material Safety Data Sheet for Ball Powder Propellant.* Retrieved November 28, 2011, from http://www.winchester.com/SiteCollectionDocuments/pdf/msds/msds_w64.pdf

Pellegrino, D., & Kirkman, C. (2011). *NATO Small Arms Ammunition Interchangeability via Direct Evidence Testing.* Retrieved June 6, 2012, from http://www.dtic.mil/ndia/2011smallarms/WednesdayInter12315Pellegrino.pdf

SCENIHR. (2008). *Opinion on the safety of medical devices containing DEHP-plasticized PVC or other plasticizers on neonates and the groups possibly at risk.*

Schafer, E., & Bowles, W. (1985). Acute oral toxicity and repellency of 933 chemicals to house and deer mice. *Archives of Environmental Contamination and Toxicology, 14*(1), 111-129.

Shirota, M. (2003). Single Dose Oral Toxicity Test of Bis(2-ethylhexyl) Azelate in Rats. *Toxicity Testing Reports on Environmental Chemicals, 11*, 287-320.

SITIS Archives. (undated). *SITIS Archives –Topic Details: Improved Stability of Double Base Propellants, available from* . Retrieved May 31, 2012, from http://www.dodsbir.net/sitis/archives_display_topic.asp?Bookmark=35270

Smyth, H., & al. (1962). Range-Finding Toxicity Data: List VI. *Amer Ind Hyg Assoc J, 23*, 95-107.

St. Marks Propellants. (1997). *Material Safety Data Sheet for Modern Smokeless Propellants* . Retrieved November 28, 2011, from http://www.wwpowder.com/data/propellants/msds/

Sutton. (2001). *Rocket Propulsion Elements.* Wiley.

Swedish Defence Materiel Administration. (1999). *Environmental Resistance Testing of Munitions.* Retrieved June 4, 2012, from http://fsd.smart-lab.se/fsd_online/pdf/english/0214e.pdf

Toxicology Regulatory Services. (2003). *Assessment of Data Availability and Test Plan for Acetyl Tributyl Phthalate (ATBC) (CAS RN 77-90-7).*

Turner, N. (undated). *Qualification and Characterisation of Nitrocellulose.* Retrieved June 4, 2012, from http://www.cranfield.ac.uk/cds/departments/deas/pdfs/1%20-%20neil%20turner,%20dosg,%20nc%20qualification%20and%20characterisation.pdf

UK Ministry of Defence. (2010). *JSP520 UK MoD's Ordance, Munitions and Explosives Safety and Environmental Management, art 2 – Guidance Leaflets including Approved Codes of Practice, Version 3.0.* Retrieved November 13, 2012, from http://www.mod.uk/NR/rdonlyres/B52CB34A-3316-4AC2-A90F-180FA14869CF/0/JSP520_Part2_Guidancev3_2webU.pdf

Unitex. (2004). Uniplex 125A - Material Safety Data Sheet.

Unitex. (2009b). *Uniplex 84.* Retrieved November 12, 2012, from http://www.unitexchemical.com/TECH_CURR/UPLX84_TECH.htm

US Army. (1989). *Military Explosives.*

US Army Defense Ammunition Center. (1998). *Propellant Management Guide.* Retrieved September 11, 2012, from http://www.scribd.com/doc/39292742/Propellant-Guide

US DoD. (2012). *Chemical & Material Emerging Risk Alert - Phthalates.* US DoD Chemical & Material Risk.

US EPA. (2012). *EPA Federal Facilities Forum: Site Characterization for Munitions Constituents* . Retrieved May 31, 2012, from http://www.clu-in.org/conf/tio/ism1/EPA-FFF-sampling-for-munitions-constituents-2011.pdf

US NTP. (2012). *N,N'-Diethylcarbanilide.* Retrieved June 4, 2012, from http://ntp.niehs.nih.gov/go/TS-85983

USP. (2009). *Material Safety Data Sheet - Tributyl Citrate.* Retrieved June 10, 2012, from http://www.usp.org/pdf/EN/referenceStandards/msds/1680608.pdf

Valenta, F. (2009). Understanding the Function of Chemical Ingredients in CADs when Pursuing "Green" Replacement Materials. *National Capital Region Energetics Symposium.*

Vertellus. (2012). *Product Name: CITROFLEX® A-4.* Retrieved June 5, 2012, from http://www.vertellus.com/product.aspx?productid=244

Wallace, J. (2008). *Chemical Analysis of Firearms Ammunition and Gunshot Residue.* USA: CRC Press (Taylor and Francis Group).

Walsh, M., & al. (2010). *Propellant Residues Deposition from Firing of 40-mm Grenades.* Retrieved June 5, 2012, from http://www.dtic.mil/cgi-bin/GetTRDoc?AD=ADA535950

Wang, H., & al. (2010). Application of Tributyl Citrate in Casting High Energy Composite Modified Double-Base Propellant with Low Smoke. *Chinese Journal of Explosives and Propellants*(5), 65-68.

Weeks, M., & McCreesh, A. (1977). *Preliminary Assessment of Relative Toxicity of Ethyl Centralite, Report no. 51-0923-77. NTIS, AD A041 736.* Aberdeen Proving Ground, MD.: Army Environmental Hygiene Agency.

Wentsel, R., Wilkinson, M., Fitzpatrick, W., Howard, W., Jones, W., & Kitchens, J. (1979). *Problem Definition Study on TAX (1-Acetylhexahydro-3,5-Dinitro-1,3,5-Triazine) SEX (1-Acetyloctahydro-3,5,7-Trinitro-1,3,5,7-Tetrazocine), Lead Salicylate and Lead P-Resorcylate 2-Nitrodiphenylamine and Ethyl Centralite, Final Report.* Retrieved June 4, 2012, from http://www.dtic.mil/cgi-bin/GetTRDoc?AD=ADA099749

WHO. (2000). *Aliphatic Primary Alcohols, Aldehydes, Carboxylic Acids, Acetals, and Esters Containing Additional Oxygenated Functional Groups, Safety Evaluation of Certain Food*

Additives and Contaminants, WHO Food Additives Series: 44. Retrieved October 25, 2012, from http://www.inchem.org/documents/jecfa/jecmono/v44jec10.htm

Wilker, S., Heeb, G., Vogelsanger, B., Petržílek, J., & Skládal, J. (2007). Triphenylamine – a 'New' Stabilizer for Nitrocellulose Based Propellants – Part I: Chemical Stability Studies. *Propellants, Explosives, Pyrotechnics, 32*, 135-148.

Wypych, G. (2004). *Handbook of Plasticizers.* ChemTec Publishing.

Zeiger, E., Anderson, B., Haworth, S., Lawlor, T., & Mortelmans, K. (1992). Salmonella mutagenicity tests: V. Results from the testing of 311 chemicals. *Environ Mol Mutagen, 19*(21), 2-141.