How to Trust a Molecule? The Case of Cyclodextrins Entering the Nanorealm

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How to Trust a Molecule? The Case of Cyclodextrins Entering the Nanorealm

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Abstract: This contribution emerged from an open, and continuing, discussion between a chemist and a philosopher, which resulted in a common awareness of the importance of trusting objects. The purpose of this biography of a molecular object – cyclodextrin – is both descriptive and normative. Descriptive: to understand how a thing can become an object of trust or/and distrust. The biography reveals three layers of valuation sustaining the process of generating trust: *reputation*, *semiosis*, and *ontology*. The first one acts at the level of actors' strategies and their interplay with regulations, the second operates with value-laden images conditioning the actors' expectations, and the last concerns the changing relationships between CD-technology and nature. As to the normative purpose, we aim at evaluating these valuations in order to allow critical trust generation. Finally, we try to appraise how nanotechnology reconfigures trust in objects by bringing visibility to the valuations.

Keywords: cyclodextrin, molecule, chemistry, biography of objects, nanomedicine, trust, confidence, Luhmann, Dewey.

Introduction

In this paper, we tell the story of a little observed yet widely applied tiny little thing, a molecule named *cyclodextrin* (CD). During the second half of the 20th century, the image of CDs has shifted from toxic yet interesting molecules to trustworthy molecules that could be used in a great number of invasive applications. In following the various objectifications of this molecule in multiple scientific communities, contexts of application and research trends, our story narrates the adventures of *trust* in cyclodextrin.

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Because of its relational and partly emotional nature, trust is an elusive concept. But it is nevertheless essential to any society. As Niklas Luhmann (1979, p. 4) put it,

> Trust, in the broadest sense of confidence in one's expectations, is a basic fact of social life. In many situations, of course, man can choose in certain respects whether or not to bestow trust. But a complete absence of trust would prevent him even from getting up in the morning.

As it will be recalled by referring to theories of trust – such as Luhmann's – it is less than obvious that one can talk about 'trust in objects': Trust is supposed to be at play only in interpersonal relationships, in which objects are mere puppets in the hands and discourse of humans. However, we will argue that some presence and depth can be allocated to objects in the generation of trust by resorting to the trope of *biography*. By making a biography of cyclodextrins, our aim is both descriptive and normative. Descriptive: to enquire into the process by which a thing *becomes* an object of trust. Normative: to critically evaluate the valuations that sustain this process. Finally, we will try to appraise how nanotechnology reconfigures trust in objects by making visible its valuations.

1. Cylodextrins

1.1. Introducing the Object

Cyclodextrins are a family of compounds made up of sugar molecules (α-D-glucopyranoside) bound together in a ring. Produced from starch (amylum) by enzymatic conversion, they are sometimes called 'cycloamyloses,' and formerly 'cellulosine' when first described by A. Villiers in 1891. The typical and most widespread CDs are the α- (6 sugar units), β- (7) and γ- (8) cyclodextrins (figure 1) which, with their truncated cone shape (figure 2), have two major properties:

- As they are hydrophobic inside and hydrophilic outside, they are able to form 'inclusion complexes' in water, i.e. they are able to 'encapsulate' another molecule in their central cavity. As a result, a hydrophobic molecule will become more soluble when 'complexed' with CDs (figure 3).
- Due to the presence of hydroxyl functions (–OH) along the molecule, they can be grafted, combined, and re-assembled with many different molecular compounds (Monza da Silveira et al., 1998; Boudad et al., 2001; Chen et al., 2009; 2010; Harada et al., 2009), including biomolecules: peptides, antibodies, proteins, vitamins, DNA, etc. (Pun et al., 2004; Davis et al., 2004; Choisnar et al., 2006; Chen and Liu, 2010).

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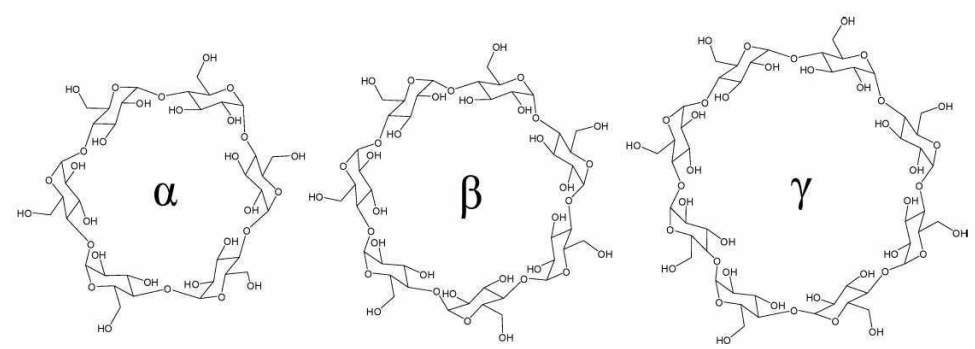

Figure 1. Chemical structure of the 3 typical native/parent CDs (Harada et al., 2009).

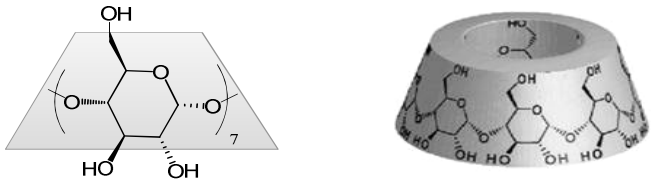

Figure 2. CDs' truncated cone shape (original picture, M. Normand).

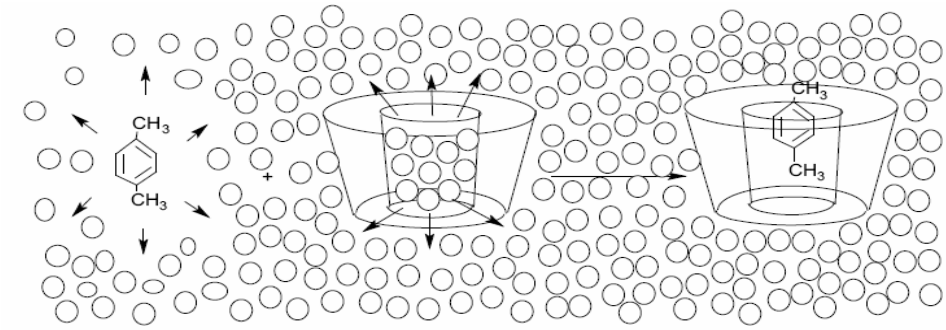

Figure 3. Formation of an inclusion complex with a hydrophobic molecule and a hydrophilic CD (Szejtli, 1998).

Due to these abilities, cyclodextrins are today perceived as 'dream molecules' for the development of applications in nanomedicine, such as targeted drug delivery systems and biosensors for molecular diagnosis (Uekama et al., 1998; Irie and Uekama, 1999; Cryan et al., 2004; Maestrelli et al., 2006; Trapani et al., 2008; Bayley et al., 2009; Couvreur et al., 2010; Ortiz Mellet et al., 2010).

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1.2. Trust Issues

How, then, can the broad concept of trust be applied to a tiny little thing such as cyclodextrin?

Trust emerged as the central issue in the course of our discussions on Mickaël Normand's own work. His Ph.D. focuses on the aim of synthesizing the prototype of a biomedical drug-release device using β-cyclodextrin. Though Normand's research is not aiming at delivering ready-to-use products for a determined therapy, it nevertheless contributes to establishing the basic synthetic route for a new generation of CD-based nanocarriers allowing time and/or site control of drug delivery in the human body. The process consists of graft polymerization of a biodegradable and biocompatible monomer to improve β-CD human-body tolerance. Normand's work can thus be seen as an attempt to develop 'safety by design' materials (Kelty, 2009; Kelty and McCarthy, 2010). But if β-CD human-body tolerance has to be improved, does that mean there is something wrong with the molecule?

We quickly acknowledged that this question could not be answered purely in terms of safety. Issues of trust stood out as a precondition for safety: Not only do scientists want their objects to be safe; they want them to be *perceived* as safe; they want objects to be trusted. But in appealing too obviously to people's confidence they risk to be mistrusted: Here is the dilemma of trust, and the very reason why trust cannot be reduced to safety, control, or security. One cannot establish trust by merely providing control, because to bestow trust implies the awareness of the trustor's vulnerability to the trustee (Baier, 1994). Whilst nanotechnology pursues the dream of achieving unprecedented control of matter and processes at the molecular scale, it seems very questionable that it could establish something as 'trust by design' on the model of 'safety by design' (by which a social preoccupation is transformed into a scientific question). Trust, unlike safety or reliability, cannot plausibly be 'embedded' in objects. It thus seems unlikely that objects could be characterized as objects of trust or distrust.

And yet, the case of CDs seems to be a counter-example. CDs are 'Generally Recognized As Safe' by the US Food and Drug Administration (FDA), and they are already widely applied for pharmaceuticals, food, cosmetics, toiletry and perfumery commodities, and even tobacco. The CD-related literature suggests, however, that CDs have raised issues of toxicity. Today, a broad consensus exists that "any of their toxic effects is of secondary character and can be eliminated by selecting the appropriate CD type or derivative or mode of application," and, as a result, that "CDs can be consumed by humans as ingredients of drugs, foods, or cosmetics" (Szejtli, 1998, p. 1743). Although chemists assume that CDs are sufficiently harmless for human consumption, they had to learn to 'fine-tune' the articulation of the molecule's toxicity levels to make CDs safe for the specific kinds of application considered. They had to establish CDs as objects of trust.

2. Historical Background

In this section we provide a historical outline of CD molecules. József Szejtli, a leading figure in the CD community, who will be discussed later, distinguished three epochs (Szejtli, 1998): a discovery period (1981-1930s); systematic studies on CDs (1930s-

1970s); and industrial production and utilization of CDs (from the 1970s onward). Because this periodization conceals important points[2], we propose a different one.

2.1. A Scientific Success (1891-1950s)

The first phase follows the standard pattern of chemical discovery: First, the extraction of a new product from a familiar material (starch); then, the discovery of interesting properties (i.e. the formation of stable complexes with organic compounds); finally, the explanation by the underlying molecular structure.

In 1891, the French microbiologist Villiers, working on the digestion of potato starch by *Bacillus amylobacter*, isolated two kinds of crystalline dextrins (i.e. derivatives of glucose) he called 'cellulosine' because they displayed properties similar to cellulose (Villiers, 1891). Then, in 1903, whilst studying microbes thought to be responsible for certain food poisoning, Schardinger reported the formation of two different crystalline products seemingly identical to Villiers' 'cellulosine:' α- and β-dextrin (Schardinger, 1903). For decades, the 'Schardinger dextrins' were studied: Pringsheim emphasised their tendency to form complexes with various organic compounds (Pringsheim, 1928; 1932). In 1936, Freudenberg and co-workers postulated cyclic structures (Freudenberg et al., 1936). 'Schardinger dextrins' became '*cyclo*dextrins'. In 1948, the same group discovered γ-cyclodextrin (Freudenberg and Cramer, 1948). At this time, the mechanism by which a hydrophobic molecule, depending on its size, can be inserted into the central cavity of CDs – thus forming an inclusion complex thermodynamically more or less stable – is elucidated and identified as a well-established structure.

2.2. From Confidence to Suspicion (1950s-1970s)

In the early 1950s, two groups took on a leading role in CD-Research: Friedrich Cramer's group in Germany and Dexter French's group in the US. While French and co-workers were working on 'many many CDs', and discovered larger molecule complexes, Cramer's group research was more specifically directed toward inclusion compounds (Cramer, 1954).

Their firm confidence in the industrial potential of CD is well attested by the first patent published by Cramer, Freudenberg and Plieninger about CD-complexation (Freudenberg et al., 1953). The patent covered practically all of the most important aspects of CD application in drug formulations (enhancement of drug's solubility and stability, protection against atmospheric oxidation, etc.) and established CDs as highly promising molecules for pharmacological applications.

Nonetheless, a couple of years later, in the first fundamental monograph on 'Schardinger dextrins' (French, 1957), French mentioned that, in some *unpublished* attempts of his group to investigate the ability of animals to metabolize β-dextrin, he had fed rats who died a week later. Was this a story forged to discredit the large patent obtained by the rival group? These results were not documented, and according to Szejtli, this review, otherwise excellent, had a huge negative impact on the image of CDs, which came to be seen as highly toxic molecules that should not be used *in vivo*. Indeed, the 1953 patent never found any industrial application (Cramer, 1987).

[2] Especially Szejtli's own role in the large-scale commercialization of CDs.

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2.3. 'Better Living With… Cyclodextrin' (1970s-2000)

Surprisingly, twenty years later, CDs came to be used everywhere, in many invasive applications, especially in Japan, and to a lesser extent in Europe and the USA.

- In the pharmaceutical field, CDs are used as excipients to improve the solubilisation and stabilization of drugs; as capsules (molecular entrapments) to enhance bio-availability and pharmacokinetics, to help avoid digestive problems, and to allow new solid phases or water-activated forms. We find CDs in vasodilators, antibiotics, anti-fungal drugs, anti-inflammatory drugs, eye-drop solutions and agro-chemicals.
- In the food industry CDs are used to encapsulate, carry and stabilize flavour, colours, vitamins and fatty acids; to sequestrate, mask or reduce undesirable taste/flavour; to lengthen chewing-gum's taste; to encapsulate 'bad' fatty acids such as cholesterol in mayonnaise and butter; to improve shelf-life of food products; to protect products against oxidation, decomposition, heat-induced or light-induced changes; and to emulsify/solubilize 'alcopops' (powder alcohol). However, with food industry, it is becoming harder to determine exactly in which products CDs are used, as unlike drugs, for which all ingredients have to be listed and registered in official pharmacopoeias, food products have no such labels.
- Cosmetics and toiletry industries were the first ones to develop CD-applications (Duchêne, 1986). It is now the biggest market[3] for CDs, which are used for 'odour control' in perfumes or laundry detergents, or can be found in shampoos to reduce their irritant effect. In the case of cosmetics and toiletry goods, the question of CD-traceability is even further complicated, because CDs are often given brand names, such as Clenzaire™, the 'secret' and almost magical ingredient of Procter & Gamble's multi-use freshener Febreze®. "Clenzaire™", an advertisement on Amazon.com reads, "is the unique new formula from Febreze® that eliminates odors on fabrics better than ever before. Clenzaire™ surrounds odors and sweeps them away, leaving your home noticeably fresh wherever you use it."
- Other uses include: tobacco industry, for the entrapment of aromas activated by combustion, and the sequestration of nicotine and tar; chemical industry, for solubilization and solidification; and textile industry, for fragrance delivery and malodor control. In Szejtli's fertile imagination, CDs could bring about a revolution in textile industry by providing 'pharmaceutical clothes' for transdermal delivery (Szejtli, 2004, pp. 1836-37).

In short, this narratives suggest that CDs entrap the 'filthiness' and make life 'more fluid'. With CDs, fats become dietetic, detergents good for you, smoking healthier...

[3] "About 70% of all cyclodextrins produced are used in this field. (…) single toiletry product, like a fragrance tissue, or a deodorant spray for furniture, curtains, or carpets, which need no health authority approval because it is not consumed by humans and is used only in laundries, requires hundreds of tons of βCD or hydroxypropyl-βCD every year" (Szejtli, 2004, pp. 1839-40).

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2.4. Supramolecular Research (from the 1990s)

In academic scientific research CDs fall under the umbrella of supramolecular chemistry[4] by epitomizing most of its core features:

- a 'host-guest system' (thanks to their ability to form inclusion complexes with a wide range of compounds);
- interlocked molecules such as catenanes and rotaxanes (Nepogodiev and Stoddart, 1998);
- scaffolds and templates to self-assemble supramolecular architectures (Easton and Lincoln 1999);
- biomimetism, with CDs mimicking "the cooperative 'multimode, multipoint' binding often observed in biological systems" (Chen and Liu, 2010).

2.5. Entering the Nanorealm (from the 2000s)

But how has nano contributed to the dream of 'wonderful' CD molecules? For one, it did not increase the number of industrial applications, which were already numerous.

In the early 2000s, the anticipated demise of the blockbuster model in pharmaceutical industry fostered intensive academic research on nanovectorization.[5] It was expected to use old active principles that have too many secondary effects or cannot go through biological barriers with classical medicines. The interest of CDs has also been emphasized in bio-sensing and DNA-chip sequencing, e.g. with individual CDs used to slow down and to measure DNA base traffic in a nanopore (Bayey et al., 2009). Besides the biomedical domain, possible uses of CDs have been reported in molecular electronics, e.g. with CDs threaded around organic conductors for the assembly of single insulated molecular wires (Anderson et al., 2002).

The nanotechnological use of cyclodextrins mainly features in the functional individualisation of the molecule. The CD molecule, or CD-conjugated molecular system, is thereby 'sold' for itself and no longer as a mere 'ingredient' in a bulk material. Especially in nanomedicines CDs are no longer excipients in a bulk formulation of the drug, but individual objects acquiring their own pharmacological identity or partaking in the production of a pharmacological effect.

3. Trust, Confidence, and Objects

So, what happened? How could the image of CDs have shifted from toxic yet interesting molecules to trustworthy molecules that could be used in a great number of invasive applications? And to what degree can we talk about trust here? To understand the

[4] According to Lehn (1987), "supramolecular chemistry may be defined as 'chemistry beyond the molecule', bearing on the organized entities of higher complexity that result from the association of two or more chemical species held together by intermolecular forces. (…) One may say that supermolecules are to molecules and the intermolecular bond what molecules are to atoms and the covalent bond."

[5] Nanovectors are not new: Their concept can be traced back to one of a 'magic bullet', proposed by Paul Ehrlich (1854-1915), known as the father of chemotherapy (Kreuter, 2007). The first development of nanoparticles for drug delivery and vaccine purposes are due to Peter Speiser and his team at ETH Zürich during the 1970s (Kramer, 1974; Kopf, 1975; Kopf et al., 1976; 1977; Marty, 1977; Marty et al., 1978).

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difficulties posed by 'trust in objects' it is necessary to make a brief incursion into *theories of trust* (Luhmann, 1979; 1988; Gambetta, 1988; Giddens, 1990; Baier, 1994; Hardin, 1996; Misztal, 1996; Nooteboom, 2002).

3.1. Theories of Trust

Most theories of trust, if not all, agree that trust is only at stake in *interpersonal relationships* when 'an agent assesses that another agent or group of agents will perform a particular action' (Gambetta, 1988). Following Luhmann, risking trust is an option that presents itself in situations of opaqueness of the other's will, whereas trust in a system or a mechanism should be called 'confidence'. Trust is deeply linked with contingency, freedom and risk. Indeed, we speak of 'trusting someone's choice,' which is contingent and subjected to uncertain opinions, whereas we speak of 'being confident in someone's knowledge,' which can only be what it is.

The distinction between trust and confidence is the basis of Luhmann's work on trust. For him, trust presupposes awareness of risk, whereas confidence does not. "Confidence, as Luhmann uses it, refers to a more or less taken-for-granted attitude that familiar things will remain stable" (Giddens, 1990, p. 31). It is involved in expectations where disappointment is a possibility that can reasonably be neglected, or avoided by filling knowledge gaps. But the difference is qualitative; it is not a matter of probability: Trust is involved where one decides to cope with the freedom of others by assuming a risk. For instance, if I buy a used car instead of a new one, I risk purchasing a dud. But here, I place trust in the salesperson and not in the car. If the car is a dud, I may regret having placed trust in someone, but I partly shoulder the blame. "The distinction between trust and confidence depends upon whether the possibility of frustration is influenced by one's own previous behaviour and hence upon a correlate discrimination between risk and danger" (pp. 31-32). According to Luhmann's definition of trust, *asking how relations of trust could be established between humans and objects would be a non-issue* or else, in the case of 'system trust', an issue of confidence.

Anthony Giddens' account of trust is more problematic, since he distinguishes between 'trust in people' and 'trust in abstract systems.' While the former corresponds to Luhmann's (1988) account of 'trust', the later is more akin to Luhmann's concept of 'confidence'. Thus, Giddens never considers fully the case of 'trust in objects', since trust is for him "a particular type of confidence rather than something distinct from it." For him, trust and confidence are connected with a more fundamental feeling of 'ontological security', where the two are not yet distinguished. But even though 'ontological security' is "a sense of the reliability of persons and things" (p. 92), it originates in the construction of personality and self-identity, *and never in the design of objects*: "Trust in the reliability of nonhuman objects, it follows from this analysis, is based upon a more primitive faith in the reliability and nurturance of human individuals" (p. 97).

A concept of trust in objects may long be searched for in the theories of trust. And if it is occasionally mentioned, it is dismissed right away. For instance,

> One can have trust in things: one's car, for example, with an expectation of performance. (…) [But] things are less interesting since they have no life or will of their own. Intentional trust does not apply. Trust associated with the actions and motivations of people, that is, behavioral trust, is more complicated, interesting and important. When the performance potential or quality of objects is difficult to judge, trust in objects may shift to trust in the provider of the object (Nooteboom, 2002, p. 55).

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To speak about trust in a nonhuman entity would be nonsense or naïve anthropomorphism. 'Trust in objects' is systematically relegated to confidence, or worst, to trust in experts: 'You can *rely* on a technology, but only *trust* experts' (Åm, 2010).

3.2. From Motivations for Trust to Objects of Trust

In order to talk about 'trust in objects', we need to decentre the focus. Such a decentring has been advocated by Trond G. Åm in a recent contribution on 'Trust in Nanotechnology' (Åm, 2010).

Åm criticizes sociological ELSI[6] surveys addressing trust in nanotechnology in terms of 'public perception': He argues that they tend to create 'forced relationships' to nanotechnology in order to compensate the lack of people's familiarity to it. For example, they may call for more involvement of lay people in the evaluation of concrete applications, which should help respondents relating nanotechnology to their everyday life, and then they measure the amount of public trust in nanotechnology. By doing so, he claims, these studies feign to predict *where* trust and distrust are likely to arise. But nano-containing products may still change name in response to public's distrust. Thus, the lability and invisibility of nanotechnology prevent these surveys from achieving the 'social robustness' they aim at.

> It is not enough to try to avoid the abstraction caused by unfamiliarity by presenting people to products 'close to everyday life'. Whereas [these studies] focus on enriching our understanding as if the entities of the relationship were given – that of nanotechnology and the public – by mapping attitudes and motivations for trust in this particular relation, the problem (…) lies in understanding how it is or becomes a relation in the first place, if at all. That is, whether it is a relation, how this relation emerges and how the establishing of the relation influences upon trust (Åm 2010).

Moreover, by presupposing that trust is something necessary and good, these surveys leave no room for a *critical* kind of trust that would work, for example, in absence of confidence, or even in combination with distrust (Poortinga & Pidgeon, 2003). Subtleties of trust are spuriously reduced to the measure of the degree of public acceptance.

Åm suggests that "the approach has to be widened and initially focus not on people's *motivations* for trust but rather the *object* of trust itself." By this, he means both:

- To reflect on the *concept* of trust, which should not be confused with acceptance, cannot merely draw upon earlier experiences in areas where there are well-defined questions, such as with GMOs or nuclear power, and cannot mean only 'participation' regardless of the qualitative features of the technology involved;
- To study "how an object of trust *becomes* an object of trust" emerging into relationships that stabilize the "character of the technology in question as an object of trust."

Åm's main point is that the human/technology relationships where trust and distrust are likely to occur cannot be considered as given. Objects of trust are worth being studied as entities that emerge into relations, and which are inherently *made of* these relationships. However, this does not tell us what may *qualify* a thing to become an object of trust, and for whom. This opens up the issue concerning *reasons* for trust.

[6] Ethical, Legal and Societal Impacts/Implications.

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3.3. Who Trusts Who and Why? A Biographical Approach Towards Objects of Trust

As Luhmann argues, we trust a person (or a thing) when we expect her (or it) to act or behave in a specific manner, although we are aware of the fact that she (or it) can act differently and frustrate our expectations. When we, nevertheless, choose to bestow trust, we do this because the trustee gives us *reasons* to trust them (or it), e.g. by their honesty, moral integrity, rationality, their previous behaviour in similar situations, and so forth. Note that this point is not about *motivations* for trust on the part of the truster (for instance friendship with the trustee), but about *reasons* to be trusted on the part of the trustee. Unlike *motivations*, reasons of trust are in connexion with the *character* of the trustee, here with the object in question.

Hence it is not enough to say that objects of trust emerge in relationships. There are some relationships that may matter more than others, or that may matter differently to different people. The problem is to know whether these relations of trust are appropriate reasons for trust, and for whom they might be so, since one of the difficulties with trust is that while one person may trust another a third will *not* because he or she does not find sufficient *reasons* to trust this person. As John Dewey put it, "a valuative judgment is therefore not a mere statement that a certain thing has been liked; it is an investigation of the *claims* of the thing in question to be esteemed, appreciated, prized, cherished" (Dewey, 1925, p. 96).

One way to address this issue – that is, to allow shifting from a descriptive to a normative account of 'trust in objects' – is resorting to Dewey's distinction between 'valuing' and 'evaluating' (Dewey, 1939). Indeed, Dewey draws at the same time a contrast and a continuum between these two kinds of valuation judgments. *Valuing* (or *prizing*) refers to one's attitude of caring for or holding precious a certain thing that one's estimates link to some consequences or/and conditions into which one holds an *interest*. Valuing thus consists of one's *situated actions* of striving to maintain, foster or procure the *estimated* conditions for the existence of this thing. Despite the personal and affective nature of the link between the valuator and the object, such a judgment is nevertheless a *behavioural attitude* that is utterly *observable*. Moreover, since the valuation is about a *certain situation* for which one infers a certain connectedness between the conditions and/or consequences that matter for oneself and the existence of the thing in question, Dewey assumes that it can be *rendered public and testable* by an *enquiry* that *brings into existence both the 'end-in-views' and objects of valuation*. Such an epistemic enquiry into the conditions, connections and possible consequences constitutes the *becoming-public* of the process of valuation; it thus tends to enable *judgments of evaluation* (or *appraising*), which are judgments *about* valuations. These "propositions *about* valuations (…) are valuation-propositions only in the sense in which propositions about potatoes are potato-propositions" (p. 39)[7]. Evaluations, or appraisals, are thus primarily concerned with the relational properties *of objects* becoming public.

Since cyclodextrins have given rise to a number of various trust-valuations by an heterogeneous array of actors, resorting to the trope of a *biography* may be a convenient method to join together the multiple voices that 'claim' the thing. *Making a biography of an object* means dealing with history as well as with memory and forgetting (Poirot-Delpech, 2009). A biography of an object is neither mere subjective account nor pure

[7] For our case study, Dewey's potato-sentence could be rephrased as follows: "[P]ropositions *about* trust-valuation of CDs are valuation-propositions only in the sense in which propositions about CDs are cyclodextrin-propositions."

succession of objective facts; it is the pragmatic construction of a narrative plot where value assignment partakes in the thing's objectification instead of being considered as a secondary projection on some objective facts; it can be construed as a 'practice of mattering' (Barad, 1998) in which humans' valuations are interwoven with the various materializations of the object. Furthermore, a biography epitomizes a certain *character*. A character (*ethos*) is a set of dispositions, e.g., of acquired tendencies to produce effects and actions in specified ways. Moulding and appraising the character of a thing is basically what any chemist does (synthesis and characterization). As characters of fiction, chemical things can acquire a consistent character while still existing in dependency of its 'characterisers': Those who manipulate them, relate to and narrate them. Last but not least, a biography of an object does not have to be an 'apology' or a 'hagiography:' It should enable *critical evaluation* of the object and of its valuations – *critical trust* (Poortinga & Pidgeon, 2003).

In our case study, cyclodextrins have been loaded with trust-valuations into both material and social processes of valuation: Material (or technical, or chemical), by chemists' achievements into tuning and modulating CDs' natural toxicity; social, by the interweaving of the valuations that built CDs' reputation, semantics and ontology. Both have contributed to rendering the character of the thing as an object that can 'pretend' to trust. Then, by bringing visibility to the trust-valuations loaded in CDs, it can be argued that CDs' entrance into the nanorealm represents a 'public test' for the evaluation of cyclodextrins.

4. The Valuations of Cyclodextrins as Objects of Trust

Our aim now is to explicate the trust-valuations that have sustained the objectifications of CDs in multiple contexts of research and use. We distinguish three different layers: *reputation* (actors' strategies and their stabilization in regulations), *semiosis* (the production of meaning through value-laden images conditioning the expectations placed in the object), and *ontology* (the changing relationships between CD-technology and nature).

4.1. Reputation

Generally, CD-development experts contend themselves with explaining the boom of CDs' application with the increasing economic availability of CDs. Within 25 years the cost of CDs dropped from $2000 to $5 per kg. This drastic price drop, combined with the mechanisms of the market, would suffice to explain CDs' diffusion in so many commodities. According to Szejtli, if the market says 'yes', then the research is good and useful.

> (...) only the decision of the market is unambiguous. Is the newly developed product or technology useful or necessary? Does it represent real development? If yes, the value of the invested work can be expressed in measurable parameters (mainly by money), if not, it will be forgotten (Szejtli, 2004, p. 1826).

If we stick to the distinction between trust and confidence, one should speak of a strong *confidence* in the market's ability to furnish an objective criterion of CD-research's value, rather than of trust. However, as simple as it seems, this rationale

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conceals at least two things: First, the way CDs became available for mass-production; and, two, Szejtli's *own role* in reshaping CDs' reputation.

For seventy years CDs could only be produced in relatively impure and small laboratory-scale amounts. In 1939, biochemists Tilden and Hudson isolated the enzyme synthesizing crystalline dextrins from starch in bacteria *Baccilus Macerans*. They predicted the possibility of using the enzyme for commercial production of dextrins[8]. But this occurred only in the 1970s when the spread of genetic engineering enabled to mass-produce CDs as pure materials from bacteria.

The first plants were built in Japan, who became the first largest world consumer of CDs in the 1970s and 1980s (Hashimoto, 2003), probably because the controversy about their toxicity found very little echo in Japan. According to Lofstson and Duchêne (2007), "in Japan, there is a tradition for industrial usage of natural products and the Japanese regarded the parent cyclodextrins as natural materials originating from starch and thus as 'non-toxic' natural products." The first CD-containing pharmaceutical product, a vasodilator[9], had been commercialized in Japan by Ono Pharmaceutical in 1976, only in 1988 in Italia[10], and then in 1997 in the USA with a formulation of β-CD in oral solution. Thus, when Szejtli entered the scene of CD-business during the 1980s, Europe and the US were lagging behind the Japanese for cultural rather than for economic reasons. In turn, this gap to be filled has brought the incentive that was just needed to stimulate the commercialization of CD-products.

József Szejtli (1933-2004) was a Hungarian chemical engineer. He has been called 'the godfather of CD', 'the designer' or 'the international harmoniser.' He organised the first CD-Symposium in Budapest in 1981. In 1985, he created a monthly newsletter surveying all CD-related literature, *Cyclodextrin News* and in 1988, wrote the first handbook on CD, *Cyclodextrin Technology*. From 1989, he was the founder and managing director of the CycloLab in Budapest, a private research organisation that became a centre for the technological transfer between CD research and industry. Without the immense efforts of this persevering man, CDs' economical value would probably not have been such great.

Szejtli's strategy to reshape CDs' reputation becomes apparent in the many reviews he wrote. The same claim can be found in at least eight of his writings: First, to remind the CD community of the 'unfounded' belief in toxicity of CDs that prevailed few decades ago; then, to denounce French's total 'misinformation', which had lead to hampering of the CD-industrial development for decades (Szejtli and Sebestyén, 1979; Frömming and Szejtli, 1994, Szejtli, 1988; 1990; 1998; 2003; 2004; 2005). Szejtli reiterated that thanks to 'adequate toxicological studies' it has been demonstrated that CDs have no inherent toxicity to inhibit their widespread utilization. However, he never referred to these 'adequate' toxicological studies except in his own seminal book (Szejtli 1988, p. 43) in which only one reference can be found: To one of his own previous studies (Szejtli and Sebestyén, 1979).

Today, several toxicological properties of CDs are known: crystal precipitation and nephrotoxicity (Rajewski et al., 1995); influence on haemolysis (Panini et al., 1996);

[8] "The preparation of the characteristic amylases of these two bacteria is a relatively simple and inexpensive procedure, and the conditions established for maximal enzyme production and starch hydrolysis provide a basis for their possible commercial usefulness. The *B. macerans* enzyme, in particular, seems to have many theoretical applications to carbohydrate chemistry which merit consideration" (Tilden and Hudson, 1942, p. 543).

[9] Prostaglandin E2/β-CD – Prostarmon E™ sublingal tablets.

[10] Piroxicam/β-CD.

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cytotoxicity (Kiss et al., 2007), among others. It is generally assumed that these effects can be masked or attenuated by using derivative (modified) CDs, and not parent (natural) ones. However, until the mid-1990s the quotation network of CDs' safety evaluation studies had still been very limited and lead in most cases to Szejtli's work.

When discussing recent and emerging nanotoxicological issues it is often stressed that current knowledge is not sufficient to deliver unambiguous answers, which, for this reason, might be decades away and available only on a case-by-case basis. Highlighting knowledge gaps is a convenient way to postpone regulatory decisions. Yet twenty years ago in CD-toxicity studies, seeking integral knowledge of toxicological properties was not the problem. Instead, as there were some already developed applications for the molecule, the method was to strengthen CDs' reputation by referring to a few, and very specific, former safe systems[11].

By the 1990s, these specific former safe systems aimed at replacing the commonly used surfactants for drug formulation that were found to cause anaphylactic reactions (Rajewski and Stella, 1996). A 'call for new formulation' was launched in order to allow the use of CDs in this pharmaceutical niche. The challenge was to allow their use for the most dangerous drug administration route: Parenteral use (injection), because it bypasses most of the body's natural defenses. Toxicological tests were crucial for this challenge. At this time, a large number of papers and reviews were produced concluding that the toxicity of CDs can be tuned by using the proper one: Either a native CD or a modified one, depending on the considered administration route. Moreover, the oral uses of CDs that had already been developed and applied, due to past 'laxity,'[12] exhorted CD-promoters to 'count the chickens before they were hatched.'[13]

But by the late 1990's, the ultimate goal was to obtain FDA approval.

> Although a number of products containing cyclodextrins have been approved for human use in Japan and Europe, no product has yet to be approved in the U.S. The approval of specific products by the Food and Drug Administration (FDA) in the U.S. will be of paramount importance to the commercial viability of cyclodextrins for worldwide pharmaceutical use (Rajewski and Stella, 1996, p. 1142).

During those years, through the production of a series of reviews, chemists and biologists in effect operated as a cyclodextrin *lobby*. In many case, these reviews would conclude like this:

> It is accepted that the lack of an approved product by the FDA has probably inhibited the universal acceptance of cyclodextrins as pharmaceutical enabling agents. We hope this mini-review has helped answer some of the questions on the issues facing the

[11] From the 1990s to today, it is the four same systems based on CD derivatives: HPβCD (2-hydroxypropyl-β-cyclodextrin), RMβCD (randomly methylated β-cyclodextrin), SBEβCD (sulfobutylether-βcyclodextrin) and HPγCD (2-hydroxypropyl-γ-cyclodextrin). As Irie and Uekama put it, "early studies showing the nephrotoxicity of the parent CDs limited administration routes (…). However, the recent availability of new CD derivatives with better safety profiles has renewed interest in extended uses of CDs administered by a variety of routes" (1997, p. 149).

[12] "Most of the currently used pharmaceutical excipients were developed several decades ago when the regulatory issues, especially regarding toxicological evaluation, were much more relaxed" (Loftsson and Duchêne, 2007, p. 8).

[13] "The industrial explorations of cyclodextrins have been hampered by toxicological evaluations, not because cyclodextrins are toxic but rather due to the high cost of proving that they are not" (Loftson and Duchêne, 2007, p. 8), followed by a reminder of French's story and by references to Szejtli's seminal studies.

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pharmaceutical development and uses of the cyclodextrins (Stella and Rajewski, 1997, p. 565).

The FDA approval was finally given in 1997. It was followed by the FDA 'Generally Recognized as Safe' (GRAS) exemptions for γ-CD (2000), β-CD (2001) and α-CD (2004). The GRAS exemption claims that the use of the molecule is exempted from the premarket approval requirements of the US Federal Food, Drug, and Cosmetic Act. In effect, it has rendered CDs immune to further regulatory toxicological issues. Indeed, although CDs are listed on Japanese, European and US Pharmacopoeias, they are mentioned in the FDA's list as 'Inactive Pharmaceuticals Ingredients.' As a result, the GRAS exemption allows CDs to be regulated as *food additives*, not as active substances. Herein lies the secret of 'the universal acceptance of cyclodextrins as pharmaceutical enabling agents.'

The process related in this section was more a self-convincing construction of the benefit of the CDs than a purely 'objective' demonstration of the abilities and innocuousness of CDs for pharmaceutical applications – hence the references to the 'objectivity' of the market mechanisms and to the respectability of the FDA approval. It was a *trust* built *for*, *by* and *amongst* the CD community while being built as a matter of *confidence* for the public.

4.2. Semiosis

As related in section *2.4*, CDs epitomized perfectly the concept of 'host-guest system' popularized by supramolecular chemistry in the 1980 to 1990s. We claim that the images and the vocabulary used by supramolecular chemistry played an important role in revaluating CDs as an *object-symbol*.

Significantly, cyclodextrins have been characterized and used as artificial chaperones (Akiyoshi et al., 2001) – natural host-guest systems that 'help' other proteins, denatured (unfolded) by thermal stress, to return to their functional state – an example of many showing how "through modifications, cyclodextrins can be invaluable in investigations at the frontiers of chemistry ranging from enzyme-like catalytic activity and antibody-like binding to aesthetically pleasing molecules" (Breslow and Dong, 1998). In supra-molecular chemistry, CDs cheerfully interweave the cognitively useful and the aesthetically pleasing.

The image of toxicity formerly associated with CD could be attenuated and superseded with connotations such as water-affinity, fluidity, softness, hospitality, stability, care and protection, the same connotations that were used for the marketing of CD-containing products such as Febreze®.[14] Thus, even if supramolecular chemistry research was mainly academic and not applied research, it helped the molecule to be positively valuated regarding its use in in-vivo applications.

Now, there is a stark contrast between the valuations of CDs conveyed by supramolecular chemistry and the valuations associated with nanovectors used for

[14] While the scientific controversy over CDs' biotoxicity seems to have come to an end, a new controversy surfaced on a different scene about what can be called the 'Febreze® rumour.' Indeed, a considerable amount of concern is expressed online about the presumed danger of the freshener regarding pets: Some people complain that their pet has been killed by Febreze®, others seek to use it in order to kill unwanted insects and domestic pests; some says that it is just an urban legend. Whether people, discussing the toxicity of their favourite household freshener, ever heard about cyclodextrins or not, the 'Febreze® rumour' looks like a lay re-enactment of 'French's rats rumour.'

targeted drug delivery: 'intrusiveness', 'stealth kill', 'nanomissiles', 'homing devices', 'one target, one bomb', 'surgical strike.'[15] Symbolized by the arrow, nanovectors rhyme with Terminators, robots programmed to kill whilst never missing their target.

Are the changing valuations attached to CDs pure rhetoric? Before criticizing these images as being value-laden, one first needs to consider their role: These images of invisible objects *are* observable valuations; they create a moral landscape that conditions the expectations actors place in the object. Following Dewey (1939), making the valuations explicit may stage the ground for their evaluation (conscious and reflexive moral judgment). However, appraising the value-laden content of these images also allows for finding better images (new valuations). For example, although the widespread used metaphor of 'homing devices' may be fully justified to the eyes of the 'crusaders' involved in the 'war against cancer', it obfuscates the very mode of operation of these objects: Indeed, with nanovectors, the formulation of a drug is no more a passive vehicle; it acquires its own kind of activity in the organism during the entire drug's trajectory. Unlike homing devices, these objects are not riveted on their target, crossing an indifferent space. They would be more like 'secret agents', designed to infiltrate a series of biological milieus by manipulating metabolic interactions in order to elude, or to cheat, immune detection and response systems. Whilst one image may be neither true nor false there are some images that are better than others. Here, the choice between the two object-symbols depends on whether one is seeking to privilege blind confidence – for the sake of therapeutic efficiency, perhaps – or critical trust.

4.3. Ontology

Moreover, these valuations involve deeper aspects that should not be neglected. Ontological features are also at stake here. All along this storyline, the relationships between CD-technology and nature are constantly reconfigured, and these changes match with various dimensions of trust (Poortinga and Pidgeon, 2003).

Arguably, starch chemists of the 1950s expressed confidence in Luhmann's sense in the industrial potential of CDs rather than trust: At the time, the boom of industrial outcomes was considered to be a kind of deterministic process. It was an expectation grounded on the natural origin of CDs, the rational knowledge of its structure-properties relationships, and its scientific success. CDs were expected to fulfil their industrial potential in the same way they had their scientific potential, and the chemists' confidence in CDs rested on a view of their 'good nature.'

However, along with confidence came suspicion: 'Natural' came to be conflated with 'toxic', and the view of CDs' 'good nature' could no longer be sustained.

This resulted in a lack of confidence – but perhaps not distrust, since it did not withdraw actions. Later on, when synthetic CDs were developed – using biological engineering, CDs were considered to be *semi-natural* products that could be trusted *if* modified in order to be safe and *if* engineered in order to serve specific applications.

Subsequently, during the rise of supramolecular chemistry, modified CDs served as simplified systems to emulate biological guest-host interactions. Re-envisioned as biomimetic systems, CDs were not merely naturalized:[16] They played the role of

[15] It is odd to notice that the concept of 'surgical strike', after having transferred from medicine to war, finally reintegrates into medicine, loaded with a bellicose meaning.

[16] A defining feature of biomimetism is that it supposes a differentiation between artefacts and their natural *analogoï* and does not mean making indistinguishable copies (Bensaude-Vincent, 2009).

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mediators between humans and nature. Furthermore, CDs were communicative tools between scientists from different fields, allowing the development of an interdisciplinary network of trust *between chemistry and biology*, and *between academic and industrial uses*. CDs became objects of trust by bridging two kinds of relationships: *human-object-nature*, and *human-object-human*.

At the same time, this resurgence of the reference to nature has resulted in a new naturalization in the CD-marketing discourse, reminding people of CDs' 'natural blessings.' It was trust stabilized and re-naturalized in confidence. Even for chemists using highly reengineered CDs, the industrial success of CDs could thus legitimately be referred to the natural origin of CDs. For example,

> Fascinating compounds including enzyme mimics, abiotic receptors, fluorescence indicators and molecular actuators, have been obtained (…). Being of natural origin, organic, biocompatible substances, CDs seem to have a unique status, and it is difficult to find any group of chemical products (drugs, cosmetics, food, plastics, paper, textiles, pesticides, etc.) or processes (formulation, catalysis, separation, stabilization, etc.) without convincing examples for the use of CDs (Bellia et al., 2009).

Finally, with all the hype and promises about nanomedicine, emphasis lies on the potential of tailor-made CDs to *overcome nature's limitations*. Of course, the wish to dispose of an indefinite number of tailored CDs enabling all possible combinations in order to achieve definite functions is not new[17], but the quest for nanovectors re-enacts it with an unequalled virulence. The attempt to get rid of nature's limitations by establishing an unprecedented control of molecular processes appeals to confidence, and even overconfidence, more than to trust.

5. How the Nanorealm Reconfigures Trust in Objects

We have argued that three layers of valuation – reputation, semiosis, and ontology – have contributed to cement CDs' character as an object of trust or distrust. On each of these layers, CDs have acquired a set of dispositions resulting from a more or less stable compromise between human strategies and material processes. Focusing on nanovectors – one particular field of nanotechnology where CDs are seen as promising – we are now aiming at appraising how nanotechnology reconfigures trust in CDs.

5.1. The Revenge of Galenics

In pharmaceutics, the 'nano-turn' concerns less *what is administered* than *the mode of administration* of the drug. In other terms, it aims at designing new *medicinal forms* rather than new drugs. It is, or it could be, a revolution in *Galenics*, not in pharmacology *per se*.

[17] 'Several chemists who have not been satisfied with what nature has provided with cyclodextrins away at this monumental task. It is to the credit of these people that a variety of new cyclodextrins are now available (…). Cyclodextrins have thus been called structural and functional straightjackets. It is a credit to those who have catapulted these unusual molecules to such prominence despite their limitations. It is mind boggling to think of the progress that could be made if cyclodextrins of any size, shape, and most importantly containing any functional groups were available' (Khan et al., 1998). Today, twelve years later, only the same four modified CDs are industrially available. Since then, the development of tailor-made CDs with properties on demand has not fulfilled its promises at all.

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Named after Galen of Pergamon (physician, surgeon and philosopher of the 2nd century), *Galenics* is the art of incorporating active principles into medicinal forms suitable for administration (pill, tablet, capsule, syrup, infusion, aerosol, inhaler, liquid injection, powder, crystal, gum, cataplasm, cigarette, etc.). Galenics has often been despised by bioscience-based pharmacology as a mere 'technical' science, or worse, as a kind of 'marketing' dealing with the drugs' 'presentation' (form, colour, encapsulation, packaging, etc.). Significantly, it is most often called 'pharmaceutical technology' in English. The external aspect given to a drug is yet crucial to introduce it in everyday life and to favour the accomplishment of the technical gestures one has to perform when taking a medicine. The Galenic form is thus essential for both the materialisation and socialisation of drugs (Rasmussen, 2005): It allows standardisation of doses, stabilisation and conservation of active substances; it has an impact on the drug release profile (bioavailability and time) as well as on its therapeutic index. Finally, it could be said that *galenics* allows transforming a mere 'drug' into a proper 'medicine.'

Functionalised nanocapsules, 'stealthy' nanovectors and other targeted drug delivery systems, are the fine flower of *galenics*. In nanomedicine, the formulation or Galenic form is designed to be fully active and involved in the drug's pharmacodynamics itself. As a result, the same drug encapsulated in a nanovector will not be bioequivalent to its non-nano counterpart – a consequence which is less due to the size[18] than to the functionalization of the mode of administration at the level of the individual therapeutic agent itself (the size being just one feature of this functional individualization). 'Molecular galenics' entails that one cannot fully distinguish between the active substance and the excipients anymore: The formulation is no longer a passive vehicle; rather, it acquires its own kind of activity in the organism during the entire drug's trajectory, e.g. by cheating on opsonization (the process by which a pathogen agent is marked for ingestion and destruction by a phagocyte), tricking protein-antibody molecular recognition, or heating magnetic particles.

5.2. The Becoming-public of Valuations

The process of functional individualization of molecular objects brings direct visibility to the valuations loaded in the otherwise invisible object. Even if they have to be interpreted and appraised, the valuations are no more hidden; they appear directly anchored to the object, gravitating around it. CDs are shown operating individually in interaction with their milieus, and are no longer a mere ingredient hidden in the bulk formulation of the drug or in the mysterious formula of a cleaning product.

While conferring new valuations to the object, the nano-realm is also operating as a discloser for past valuations. Suddenly, the object's trajectory is rendered visible. For that reason, a biography of cyclodextrins may not have been possible before they became 'nano'. If nanotechnology renders the invisible visible, it does not show it as something that was sitting there for ever; but rather as something that is manifestly half natural, half made on purpose, and raises the question of its finality. By accomplishing their 'nano-turn', molecular objects appear somewhat overtly with their valuations. Contrarily to the norm that prevailed in the self-image of modern science, in the technoscientific nanorealm the objectivity of the object and the values of its uses are no longer separated. This makes a huge difference regarding the generation of trust: Trust-valuations become

[18] If we consider the size of a bulk formulation of a drug, a nanovector would be smaller, but if we consider the size of a therapeutic molecule alone, it is in fact bigger than it.

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somewhat *publicly observable*, and not only limited to scientists, industrials and experts. The schema 'trust in the scientific community *versus* confidence for the public' does no longer seem acceptable.

5.3. The Need for Critical Trust

But the problem is not participation *per se*; it is not that laypeople *necessarily have to* be involved in upstream engagement, regardless of the character of the technology in question. The problem is object-centred: Becoming 'nano' reconfigures the character of chemical objects. Nano-objects acquire a mode of existence that, in order to be brought to completion, appeals to be socially invested and critically appraised. Nano-objects cry out for critical trust.

The new meanings and valuations acquired in the nanoworld may be in contrast or in conflict with past valuations. Consider drug formulation when becoming 'nano:' Traditionally, as Galenics is based on the coupling between the active principle and the formulation, it allows mediating the chemical and the social (Rasmussen, 2005). In nano-medicines, it cannot guarantee this social function anymore. Unlike traditional galenics, with nanomedicines the materialisation and the socialisation of the drugs are not occurring at the same scale anymore. Mediation is missing, and has to be reinvented. New mediations, new valuations have to be found.

It is important for the purpose of regulation to take into account both the added values and the reactivation of past valuations. Consider, for example, the regulatory GRAS exemption, allowing CD to be regulated as a food additive. Is it still relevant for CDs used in nanomedicines? The concept of nanomedicine requires an re-evaluation of classical substances that were previously considered to be simple ingredients and that are now designed to be fully active, with every single molecule having a well-defined function, contrary to our present medicines operating only following statistic laws; and turning CDs into active substances would require a new approval and the end of the GRAS exemption.

6. Conclusion

This paper advocates the notion of 'trust in objects' which is taken into account neither by the social theories of trust nor by nanotechnology ELSI studies, which approach trust in terms of 'public perception' (Åm, 2010).

We argue that *human/objects relationships do involve trust* and not just confidence. Our case study shows that a firm distinction between trust and confidence can be maintained, although they work together. For instance, confidence, or perhaps over-confidence, is obvious in Szejtli's repeated criticisms of French's misinformation as if he had betrayed the cause of CDs. The attempt at producing confidence is also obvious in the series of reviews emphasizing the innocuousness, availability and advantages of CDs for pharmaceuticals and chemists, even if the CD community was first bestowing trust and only thereafter 'selling' confidence.

Does an object become an object of trust 'by design?' To be sure, technical (or chemical) design can contribute to the construction of trust, but no design can *secure* trust. Trust, unlike reliability, is never acquired once for all. And there is no trust without the awareness of a risk. Ironically, Szejtli's repeated claims for the innocuousness of CDs contributed to keeping alive the memory of toxicity.

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Trust should not be overestimated as a moral or normative concept. Neither should it be confounded with trustworthiness (Hardin, 1996) nor mere acceptance. Consequently, what has been described as an 'object of trust' is not necessarily a 'good' object (while an object of distrust would be a 'bad' one). However, it is no longer a neutral object. It is not 'beyond good and evil', but would be more *below* good and evil. It would be an object that has *acquired* the ability to be called an object of trust or/and distrust.

This opens up issues concerning public debates: Rather than to be focused on acceptance, or on the ways to gain public's confidence, should public debate reflect fully and explicitly the valuations sustaining the subtle mechanisms of trust? How can this be accomplished without provoking a general feeling of 'ontological insecurity?' To which extent should public trust be transmuted into public confidence by 'black boxing' the values in the objects? How and who is to decide that? And, what could be a desirable 'economy of trust and confidence' for nanotechnology?

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