WHITE PAPER

# U.S. FDA'S FOOD CONTACT NOTIFICATION PROGRAM AND FOOD-GRADE LUBRICANTS: WHAT THE GUIDELINES DON'T TELL YOU

Lubricants used in food contact applications, also known as food-grade lubricants, are ubiquitous in food processing environments where incidental contact between the lubricant and food products may occur. Although some ingredients in food-grade lubricants are covered in existing regulations, many ingredients are unregulated. In 2000, the U.S. Food and Drug Administration (FDA) began the food contact notification (FCN) program to give manufacturers the opportunity to notify the FDA on the safety of unregulated substances used in food contact materials (including food-grade lubricants) prior to placing them in the market. Although the FDA has published guidelines on how to prepare FCNs, much of the content in these guidelines does not apply to food-grade lubricants. This white paper reviews the most critical data requirements (based on first-hand experience) for FCNs as they pertain to lubricants and highlights some of the most common issues that arise when preparing such an FCN. Special considerations that are specific to food-grade lubricants are also discussed.

## BACKGROUND

Food-grade lubricants intended for use in food processing applications are regulated by the FDA in Title 21 of the U.S. Code of Federal Regulations (21 CFR § 178.3570), which contains a list of allowable ingredients with corresponding purity requirements and use level limitations. Thus, one way to show that a food-grade lubricant may be safely used on machinery is to verify that the lubricant contains only ingredients that either comply with 21 CFR § 178.3570 or are generally recognized as safe (GRAS) for direct addition to food; however, this regulation has not been amended for several decades and many food-grade lubricants on the market today are comprised of base oils and additives that do not meet these formulary requirements. Since adding to or amending 21 CFR § 178.3570 requires a food additive petition, a process that involves a review period of over two years, most food-grade lubricant manufacturers utilize the FDA's FCN program to satisfy their regulatory obligations when the formulation of the food-grade lubricant does not comply with 21 CFR § 178.3570.

Generally speaking, an FCN must be submitted to the FDA for an unregulated food contact substance (FCS). An FCS is defined as "any substance that is intended for use as a component of materials used in manufacturing, packing, packaging, transporting, or holding food if such use of the substance is not intended to have any technical effect in such food." In other words, an FCS can be loosely defined as a chemical substance that may be expected to migrate into food from a material that comes into direct contact with food (typically food packaging). An FCN may apply to only a single chemical substance or FCS, meaning that the FCN may only apply to a single ingredient in a food-grade lubricant (e.g. a single base oil or a single additive such as an antioxidant), but not the whole lubricant. So if there are two or more unregulated ingredients in the food-grade lubricant, separate FCNs must be submitted for each. Furthermore, when an FCN is acknowledged by the FDA without objection, it is only applicable to the manufacturer of the FCS. This aspect of the FCN submission can be seen as advantageous because a manufacturer that produces the same unregulated FCS cannot "piggyback" off another manufacturer's FCN.

The content of an FCN must include a wealth of information that completely addresses three key characteristics of the FCS: its chemical identity and impurity profile, its expected level of exposure in consumers based on the intended use and its toxicological profile. To date, nearly 2,000 FCNs have been submitted for a wide range of FCSs in various food contact materials. Approximately 70% of these submissions resulted in a successful acknowledgement from the FDA at the end of the process, whereas unsuccessful FCNs often fail to adequately describe one or more of these three characteristics. Notably, only 35 of the over 1,400 successful FCNs listed on the FDA's inventory of effective food contact substance notifications are applicable to food-grade lubricants. In addition, existing FDA guidance documents relevant to the preparation of FCNs (cited at the end of this paper) pertain primarily to food packaging applications and do not address any special considerations for evaluating food-grade lubricants. The relative lack of common experience and authoritative guidance specific to food-grade lubricants therefore presents a special challenge when planning for a successful FCN submission.

## FCN ITEM 1: ESTABLISHING THE CHEMICAL IDENTITY AND IMPURITY PROFILE

When beginning the preparation of your FCN, establishing the chemical identity of your food-grade lubricant FCS begins by clearly stating basic information, including the chemical name and Chemical Abstracts Service (CAS) registry number for the FCS, as well as providing a representative chemical structure. Two other critical questions that are addressed in this part of the FCN are:

1. Does the chemical identity of the FCS match the chemical name/descriptor stated on the FCN application?
2. What are the chemical identities of each impurity in the FCS and exactly how much of these impurities remain in the FCS?

Although there are no specific guidelines on the extent of analytical chemistry data required to verify the chemical identity of the FCS to address question 1, there are several common elements typically associated with successful FCNs for food-grade lubricants. Typically, analysis of the chemical identity of the FCS is conducted with Fourier-transform infrared spectroscopy (FTIR) or nuclear magnetic resonance (NMR). Analysis is also typically conducted for at least three separate production batches of the FCS to ensure that the results indicate consistency from batch to batch. When reporting the results of these analyses in your FCN application, it is essential to include the following information:

- The analytical methodology, including the equipment used (make and model of spectrometer, settings used), a description of the software used in the analysis and details on how samples were prepared and injected into the machine
- Full graphical readouts of the FTIR or NMR spectra for each batch tested
- Labeling of all major peaks, indicating which chemical functional group(s) are associated with each of the major peaks
- Written description of how the results of the analyses support the stated chemical description of the FCS

For food-grade lubricants, failure to adequately characterize the impurity content of the FCS (i.e. question 2) is one of the most common problems associated with an unsuccessful FCN. This is for a good reason: In the complex matrix associated with a typical lubricant base oil, impurities can be difficult to definitively identify and even more difficult to quantify, particularly for complex reaction products in which the FCS may consist of a complex mixture of various chemical substances. Approaching this aspect of the FCN successfully begins with a detailed description of the manufacturing process (a required component of the FCN). In this description, it is especially important to identify the starting materials (reactants) and all intermediate production aids involved.

> Analysis for impurities should focus on detecting and quantifying any residual unreacted starting materials or intermediate processing aids as described in the manufacturing process. This may be done by performing gas chromatography/mass spectroscopy (GC-MS) or other applicable methods (such as gas chromatography/flame ionization detection (GC-FID)) using appropriate reference standards. At least three production batches should be analyzed. For all analyses, be sure to include the following information:

- The analytical methodology, including the equipment used (make and model of spectrometer, and settings used), a description of the software used in the analysis, details on how samples were prepared and injected into the machine, and a description of calibration methods
- All applicable raw data, including full graphical readouts of the GC-MS chromatograms and calibration curves
- A description of how each impurity was quantified using the data available (showing mathematical calculations, if possible)
- In cases where a residual starting material or intermediate processing aid was not detected, identification of the appropriate detection limit associated with the method as well as a description of how the detection limit was calculated
- A written description of how the method was validated (i.e. any testing conducted to show that the method you used can accurately detect the impurities of interest) and any supporting data

In addition, any other unexpected impurities that are detected during the analytical chemistry evaluations that cannot be traced to one of the starting materials or intermediate processing aids should also be characterized (as fully as possible) and quantified. If there are any unexpected impurities that cannot be fully characterized, it is advisable to provide the best chemical description possible, since the inability to fully characterize one or more impurities may still be acceptable if exposure levels are anticipated to be sufficiently low.

## FCN ITEM 2: CONDUCTING THE EXPOSURE ASSESSMENT FOR THE FCS AND ITS IMPURITIES

Another requirement for all FCNs is to calculate the dietary concentration (DC) and estimated daily intake (EDI) associated with the intended use of the FCS. This helps determine the extent of the safety data that is required to support your FCN. The DC is simply the expected level of contamination, expressed as the amount of FCS per amount of food (e.g. µg/kg or parts per billion). The EDI is the expected amount of FCS consumed by a typical person in a day, expressed as amount of FCS per day (e.g. µg/day). To calculate the EDI from the DC, the DC is multiplied by a factor of 3 (this is based on the assumption that a typical person consumes 3 kg of food per day). It is also important to calculate the DC and EDI for both the FCS and the impurities. To calculate the EDIs for the impurities, it is typically sufficient to multiply the EDI you calculated for the FCS by the maximum percent by weight of each impurity.

Although the applicable FDA guidelines on the preparation of FCNs include detailed recommendations for utilizing migration test results to calculate dietary concentrations for FCSs associated with food packaging materials, no guidelines have been provided for calculating DCs associated with ingredients in food-grade lubricants. Therefore, one significant challenge associated with preparing an FCN for food grade lubricants is to conduct an exposure assessment based on a reasonable-use scenario that is reasonably conservative, but not excessively so. This challenge is often compounded by the fact that lubricant manufacturers (or manufacturers of lubricant ingredients) cannot always anticipate all possible food-related uses associated with downstream users.

Unfortunately, to date there is no published data or any other reliable sources of information regarding typical amounts of food-grade lubricants that come into direct contact with food in a typical-use scenario. Thus, based on contamination limits specified in 21 CFR § 178.3570, the default approach is to assume that the finished lubricant contaminates food at a level of 10 parts per million (ppm). In other words, assume that the DC for the finished lubricant is 10 mg lubricant per kg food. At this level of contamination, unless the FCS is present in the lubricant at a very low use level (equal to or less than 0.5% by weight), a substantial amount of safety data (see FCN item 3 below) is required to support the FCN. Therefore, it is beneficial to do the necessary research to devise a robust exposure assessment for the purpose of refining the DC calculation to a more realistic amount, enabling you to avoid the unnecessary time and cost associated with additional unnecessary safety studies. When doing this, some important questions to consider include:

- What is the maximum use level of the FCS in the finished lubricant?
- Will the lubricant be used in all types of food processing facilities? Or will it be restricted to use only in specific applications (e.g. on a beverage conveyer belt, in a bakery oven, in a meat packaging facility, etc.)?
- What is the typical application rate of the finished lubricant (amount applied per year)?
- How many kilograms or pounds of the applicable food type(s) is typically processed per year at a representative food processing facility?
- If applied to a conveyer belt, what fraction of the conveyer length carries unsealed food that could be exposed to the lubricant?

Knowing all or even some of this information can help you calculate a more realistic DC and EDI. For example, if it is known that the lubricant is only used in baking applications, the EDI can be reduced by the fraction of a person's daily diet that typically consists of baked food.

If the application rate of the lubricant and the amount of food processed in a representative facility are known, then the DC can be reduced by the ratio of total lubricant applied per year to total amount of food processed per year. Furthermore, if you have sufficient knowledge of the food processing applications that are relevant to the lubricant, it may be possible to estimate the fraction of the total lubricant applied that could possibly be exposed to uncovered food during the process. This avoids the necessity of assuming an unrealistic worst-case scenario where all of the applied lubricant could contaminate food. If you do not know any of this information because you sell your lubricant to downstream users, it may be helpful to conduct a survey of a representative sample of downstream users to obtain this information.

As a last resort, it may be helpful to consider applying a market volume limitation (MVL) to your DC/EDI calculation. The concept of the MVL arises from the fact that a typical DC/EDI calculation for a food-grade lubricant assumes that all the food a person consumes in a given day was processed at a facility where a food-grade lubricant containing the specific FCS in question is being used. For example, perhaps your FCS is a unique base oil that is only expected to penetrate 5% of the total U.S. market for food-grade lubricants. In that case, it would be reasonable to assume that only 5% of a person's total daily diet (on average) could possibly be exposed to the FCS, thereby allowing you to reduce your DC and EDI by a factor of 20 (using a 5% reduction factor).

The FDA is likely to ask for supporting information to justify a stated MVL. Such evidence may consist of up-to-date market survey data verifying the size of the food-grade market in the U.S. (e.g. number of tons of food-grade lubricants sold per year) as well as market data showing that the market penetration of food-grade lubricants containing the FCS of interest does not exceed a certain percent of the total food grade lubricant sector. In summary, if you get to a point where you need to rely on an MVL to help refine and reduce your DC and EDI, you should be prepared to support your stated MVL using current market data specific to food-grade lubricants.

As if all this was not complicated enough, there is yet one additional concept related to exposure that needs to be mentioned: the cumulative estimated daily intake (CEDI) to account for multiple sources of exposure to the FCS. Consider a scenario in which Company A is submitting an FCN for a lubricant colorant that is also regulated in 21 CFR for use as a colorant in food-contact plastics. In this case, Company A must consider the cumulative exposure to the colorant resulting from both its use as a lubricant antioxidant and as an antioxidant in plastics. When the CEDI must be adjusted to account for another regulated use of the FCS, as in Company A's scenario, the EDI associated with the regulatory use can usually be found in the FDA's CEDI database (available online). Thus, the EDI associated with the regulatory use and the EDI associated with the proposed lubricant use must be added to obtain the CEDI. Next, consider another scenario in which Company B is submitting an FCN for a lubricant base oil. Company B subsequently notices that Company C has previously submitted an FCN for the same base oil and same end use. In Company B's scenario, the FDA would probably consider both companies' lubricants to be substitutional since the end uses are identical. Therefore, the EDIs associated with these two FCNs do not need to be added to obtain the CEDI, provided that Company C's EDI was not based on an MVL. Lastly, if there are no other regulated food contact uses associated with the FCS and the FCS is not the subject of another effective FCN, then the CEDI is simply equal to the EDI.

In summary, when conducting the exposure assessment for the food-grade lubricant FCS and its impurities in the absence of any authoritative guidance specific to lubricants, you should leverage the most detailed end-use information available to prevent calculating exposure estimates that are excessively conservative. The calculations should be clearly shown as a separate attachment to your FCN application, with detailed explanations of all parameters and assumptions used in the calculation. The written description should include clearly-stated DCs, EDIs and CEDIs for the lubricant FCS and all relevant impurities.

## FCN ITEM 3: TOXICOLOGICAL PROFILE OF THE FCS

In this section of the FCN, you need to provide data to show that the FCS and its impurities are safe at the CEDI you calculated in the previous section. The basic idea is that as the CEDI for the FCS increases, more safety information is required to support your FCN. It is important to remember that, just as separate CEDI calculations are required for the FCS and its impurities, separate toxicological profiles are also required for both the FCS and its impurities. The FDA requires the safety information on your FCS to be presented in two parts. The first is the comprehensive toxicological profile, where you provide detailed summaries of the methods and results for each relevant safety study for both the FCS and each impurity. The second part is the safety narrative, in which you provide a detailed discussion of the safety data, including your interpretation of the results of the relevant safety data and how the safety data allows you to conclude that the FCS and its impurities are safe for the intended use.

In previous FCNs submitted for FCSs in food-grade lubricants, the CEDIs were typically 150 µg/person per day or less. At this exposure level, the recommended safety data to support the FCN consists of: (a) a test for gene mutations in bacteria and (b) an in vitro test with cytogenetic evaluation of chromosomal damage using mammalian cells or an in vitro mouse lymphoma tk± assay. These tests are screening-level assays that help predict whether the FCS may have carcinogenic potential. They are routinely performed by toxicology testing laboratories and are relatively inexpensive when compared with other toxicological tests, particularly those involving live animals. It should be noted that interpreting the results of these studies may require some toxicological expertise, particularly if there is a positive result. A clear positive result in any one of these assays may necessitate much more expensive toxicological testing, so it is important to use sound professional

judgment when interpreting the results of these tests.

One important point to consider is that when the CEDI is greater than 150 µg/person per day, a substantial amount of animal testing is required in addition to the genetic toxicity screening-level data previously described: namely, two 90-day sub-chronic repeated dose studies (one in a rodent species and one in a non-rodent species). Considering the substantial cost associated with conducting these studies and the considerable expertise required to interpret their results, ensuring that the CEDI for the FCS does not exceed this threshold is beneficial. If the CEDI does exceed this threshold, consider obtaining additional end-use information to further refine the CEDI calculation. You can also consider whether reducing the use level of the FCS in the finished product is a possible option, before committing to investing in this additional testing.

Another point to mull over is the importance of searching for relevant safety data that already exists before investing in your own safety testing. For example, you should search the FDA's inventory of effective FCNs for food contact substances to determine whether another FCN has previously been submitted for an FCS that has the same chemical identity as your FCS. If this is the case, it is possible that the safety data submitted for the previous FCN can be utilized to support your own FCN without the need for new safety data. Unfortunately, the only way to determine this with certainty is to obtain the relevant safety data associated with the previous FCN. This requires submitting a Freedom of Information Act (FOIA) request to the FDA to obtain the data. Submitting the FOIA request is simple and can be done through the FDA's website. Just be sure to specify the exact records you are looking for (e.g. "toxicological studies submitted in support of FCN XXX"). Once the relevant safety studies have been obtained, they can be reviewed to determine whether they can be used to support the safety of your own FCS.

There are some differences in the approach when considering the safety of the impurities. This is largely because in most cases, the CEDIs associated with the impurities are very small, usually less than 1.5 µg/person per day depending on the level of impurities detected in your analytical chemistry analysis. When the CEDI is less than or equal to 1.5 µg/person per day, no safety studies are required; however, it is still necessary to evaluate the potential carcinogenicity of the impurity. A source of relevant safety information may be published scientific literature that can be searched using the PubMed database. If no information can be found regarding the potential carcinogenicity of a certain impurity, it is enough (in most cases) to describe your literature search process and results, stating that "insufficient information was identified in the public domain to evaluate the carcinogenicity of the impurity." The use of in-silico tools, such as quantitative structural activity relationships (QSARs), may also be useful to determine if the molecular structure of the impurity contains any functional groups that indicate a specific carcinogenic hazard. Nonetheless, any QSAR-based evaluation should be conducted and summarized by a trained toxicologist. Lastly, a situation in which one or more impurities are present in the FCS that were unable to be fully characterized using appropriate analytical chemistry methods may be acceptable if it can be clearly shown that the CEDIs are less than or equal to 1.5 µg/person per day and an educated inference can be made as to the general class of compounds to which the impurity belongs. In that case, it may be useful to discuss the potential carcinogenicity of the class of compounds as a whole.

In general, if the weight of evidence indicates that the impurity itself–or the class of compounds to which the impurity belongs–has concerns for carcinogenic effects in mammals, then the safety narrative for the impurity should include a quantitative risk assessment written by a trained toxicologist.

## THRESHOLD OF REGULATION (TOR) EXEMPTIONS

If you were able to show that the DC for your food-grade lubricant FCS is less than 0.5 ppb, you may want to consider a TOR exemption rather than an FCN to fulfill your regulatory obligation for the unregulated FCS. One advantage of submitting a TOR exemption instead of an FCN is that no data is required to verify

the chemical identity for multiple batches and very little safety data is required. To address safety, it is usually sufficient to perform a literature search for the FCS and all impurities, verifying that no data exists to suggest the FCS or its impurities are associated with any cancer hazard. The major disadvantage, however, associated with the TOR exemption is that once the TOR exemption is acknowledged by the FDA and listed in its inventory, another company making a lubricant containing the same FCS can "piggyback" off your TOR exemption without having to submit its own TOR exemption. Therefore, the extra effort associated with the FCN compared to the TOR exemption may be worth it to obtain that extra competitive advantage.

## CLAIMING EXCLUSION FROM THE REQUIREMENT TO COMPLETE AN ENVIRONMENTAL ASSESSMENT (EA)

It is easy to miss this requirement. According to the applicable regulations, an EA must be completed for all FCSs unless it meets the requirements for a "categorical exclusion." In most cases, for food-grade lubricants this simply requires checking the appropriate boxes on the application form to claim the appropriate categorical exclusion. More specifically, you want to claim categorical exclusion under 21 CFR 25.32(j), in which you specify that the lubricant is not a component of a repeat-use article, but rather a component of a permanent or semi-permanent food contact surface. Finally, be sure to check the appropriate boxes on the application form indicating that the proposed food contact use complies with the categorical exclusion criteria and, to the best of your knowledge, there are no extraordinary circumstances that would require you to submit an EA. For most food-grade lubricants, claiming the categorical exclusion from the requirement to submit an EA is straightforward; however, bear in mind that if your end use description does indicate there could be an environmental impact (e.g. a significant amount of used lubricant is expected to drain into wastewater streams), the FDA may object to your categorical exclusion claim. In this case, you would need to complete an EA.

## CONCLUDING REMARKS

The preparation of an FCN for an ingredient (FCS) in a food-grade lubricant involves the consideration of several factors that are not addressed in existing FDA guidance documents. Most importantly, since no guidelines exist for evaluating consumer exposure to food-grade lubricants, obtaining both qualitative and quantitative information on how the lubricant is used is critical to acquiring realistic exposure estimates. Another critical component of a successful FCN for a food-grade lubricant is a robust analytical chemistry analysis to determine and quantify the impurity profile. In addition to the FCS itself, each impurity can be addressed in the exposure calculations, comprehensive toxicology profile and safety narrative. Looking ahead, a well conducted study of the distribution of empirical lubricant contamination levels in various food types, as the result of food processing applications, would be of utmost importance toward replacing the use of the default assumption that a typical food grade lubricant contaminates food at a concentration of 10 ppm.

By effectively planning and ensuring the critical components discussed in this white paper are fully addressed, you can substantially increase the odds of success associated with your FCN application. Furthermore, it should hopefully save you time and money during the application process as well.

## ABOUT THE AUTHOR

Brad Lampe is a Principal Toxicologist at NSF International and has been a member of its toxicology department since 2007. After joining NSF's risk assessment team full-time in January 2015, Mr. Lampe authored and successfully defended 15 chemical risk assessments related to unregulated drinking water contaminants. He has also presented his work at domestic and international professional conferences. In addition, Mr. Lampe is an expert in the regulation of food additives and dietary ingredients in the U.S. and in the regulation of cosmetic products in the European Union. Besides successfully preparing and submitting numerous regulatory submissions for new indirect food additives on behalf of NSF's clients, he has led several training sessions and webinars on the topic of new dietary ingredients. Mr. Lampe has also authored several articles related to chemical risk assessment.

## USEFUL REFERENCES


1. Guidance for Industry: Preparation of Food Contact Notifications (Administrative).
2. Guidance for Industry: Preparation of Premarket Submissions for Food Contact Substances (Chemistry Recommendations).
3. Guidance for Industry: Preparation of Food Contact Notifications for Food Contact Substances (Toxicology Recommendations).
4. Guidance for Industry: Submitting Requests under 21 CFR 170.39 Threshold of Regulation for Substances Used in Food-Contact Articles.
5. Inventory of Effective Food Contact Substance (FCS) Notifications.
6. Threshold of Regulation Exemptions for Substances Used in Food-Contact Articles.
7. CEDI Database.
8. CFR – Code of Federal Regulations Title 21 Part 178, Sec. 178.3570: Lubricants with incidental food contact.



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